Appendix B

U.S. Pat. Appl. No. 09/518,501

Erion, *et al.*

Copegus—Cont.

aged and scarred. This is called cirrhosis. Cirrhosis can cause the liver to stop working. Some people may get liver cancer or liver failure from the hepatitis C virus.
Hepatitis C virus is spread from one person to another by contact with an infected person's blood. You should talk to your healthcare provider about ways to prevent you from infecting others.

How should I store COPEGUS?

Store COPEGUS tablets at room temperature (77 °F).
Please refer to the PEGASYS Medication Guide for storage information about PEGASYS injection.

General information about the safe and effective use of COPEGUS

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use COPEGUS for a condition for which it was not prescribed. Do not give COPEGUS to other people, even if they have the same symptoms that you have.
This Medication Guide summarizes the most important information about COPEGUS. If you would like more information, talk with your healthcare provider. You can ask your healthcare provider or pharmacist for information about COPEGUS that is written for healthcare professionals.

What are the ingredients in COPEGUS?

Active Ingredient: ribavirin
Inactive Ingredients: pregelatinized starch, sodium starch glycolate, cornstarch, microcrystalline cellulose, and magnesium stearate. The tablet is coated with aquacoat ECD-30, triacetin, and colored with a coating system composed of hydroxypropyl methyl cellulose, talc, titanium dioxide, synthetic yellow iron oxide, and synthetic red iron oxide.
This Medication Guide has been approved by the U.S. Food and Drug Administration.

CYTOVENE®-IV

℞

(ganciclovir sodium for injection)
FOR INTRAVENOUS INFUSION ONLY

CYTOVENE®

(ganciclovir capsules)
FOR ORAL ADMINISTRATION

The following text is complete prescribing information based on official labeling in effect June 2000.

WARNING: THE CLINICAL TOXICITY OF CYTOVENE AND CYTOVENE-IV INCLUDES GRANULOCYTOPENIA, ANEMIA AND THROMBOCYTOPENIA. IN ANIMAL STUDIES GANCICLOVIR WAS CARCINOGENIC, TERATOGENIC AND CAUSED ASPERMATOGENESIS. CYTOVENE-IV IS INDICATED FOR USE *ONLY* IN THE TREATMENT OF CYTOMEGALOVIRUS (CMV) RETINITIS IN IMMUNOCOMPROMISED PATIENTS AND FOR THE PREVENTION OF CMV DISEASE IN TRANSPLANT PATIENTS AT RISK FOR CMV DISEASE.
CYTOVENE CAPSULES ARE INDICATED *ONLY* FOR PREVENTION OF CMV DISEASE IN PATIENTS WITH ADVANCED HIV INFECTION AT RISK FOR CMV DISEASE, FOR MAINTENANCE TREATMENT OF CMV RETINITIS IN IMMUNOCOMPROMISED PATIENTS, AND FOR PREVENTION OF CMV DISEASE IN SOLID ORGAN TRANSPLANT RECIPIENTS (see INDICATIONS AND USAGE).
BECAUSE CYTOVENE CAPSULES ARE ASSOCIATED WITH A RISK OF MORE RAPID RATE OF CMV RETINITIS PROGRESSION, THEY SHOULD BE USED AS MAINTENANCE TREATMENT ONLY IN THOSE PATIENTS FOR WHOM THIS RISK IS BALANCED BY THE BENEFIT ASSOCIATED WITH AVOIDING DAILY INTRAVENOUS INFUSIONS.

DESCRIPTION

Ganciclovir is a synthetic guanine derivative active against cytomegalovirus (CMV). CYTOVENE-IV and CYTOVENE are the brand names for ganciclovir sodium for injection and ganciclovir capsules, respectively.
CYTOVENE-IV is available as sterile lyophilized powder in strength of 500 mg per vial for intravenous administration only. Each vial of CYTOVENE-IV contains the equivalent of 500 mg ganciclovir as the sodium salt (46 mg sodium). Reconstitution with 10 mL of Sterile Water for Injection, USP, yields a solution with pH 11 and a ganciclovir concentration of approximately 50 mg/mL. Further dilution in an appropriate intravenous solution must be performed before infusion (see DOSAGE AND ADMINISTRATION).
CYTOVENE is available as 250 mg and 500 mg capsules. Each capsule contains 250 mg or 500 mg ganciclovir, respectively, and inactive ingredients croscarmellose sodium, magnesium stearate and povidone. Both hard gelatin shells consist of gelatin, titanium dioxide, yellow iron oxide and FD&C Blue No. 2.
Ganciclovir is a white to off-white crystalline powder with a molecular formula of $C_9H_{13}N_5O_4$ and a molecular weight of 255.23. The chemical name for ganciclovir is 9-[[2-hydroxy-1-(hydroxymethyl)ethoxy]methyl]guanine. Ganciclovir is a polar hydrophilic compound with a solubility of 2.6 mg/mL in water at 25°C and an n-octanol/water partition coefficient of 0.022. The pK_as for ganciclovir are 2.2 and 9.4.
Ganciclovir, when formulated as monosodium salt in the IV dosage form, is a white to off-white lyophilized powder with a molecular formula of $C_9H_{12}N_5NaO_4$, and a molecular weight of 277.22. The chemical name for ganciclovir sodium is 9-[[2-hydroxy-1-(hydroxymethyl) ethoxy]methyl]guanine, monosodium salt. The lyophilized powder has an aqueous solubility of greater than 50 mg/mL at 25°C. At physiological pH, ganciclovir sodium exists as the un-ionized form with a solubility of approximately 6 mg/mL at 37°C.
All doses in this insert are specified in terms of ganciclovir.

VIROLOGY

Mechanism of Action: Ganciclovir is an acyclic nucleoside analogue of 2'-deoxyguanosine that inhibits replication of herpes viruses. Ganciclovir has been shown to be active against cytomegalovirus (CMV) and herpes simplex virus (HSV) in human clinical studies.
To achieve anti-CMV activity, ganciclovir is phosphorylated first to the monophosphate form by a CMV-encoded (UL97 gene) protein kinase homologue, then to the di- and triphosphate forms by cellular kinases. Ganciclovir triphosphate concentrations may be 100-fold greater in CMV-infected than in uninfected cells, indicating preferential phosphorylation in infected cells. Ganciclovir triphosphate, once formed, persists for days in the CMV-infected cell. Ganciclovir triphosphate is believed to inhibit viral DNA synthesis by (1) competitive inhibition of viral DNA polymerases; and (2) incorporation into viral DNA, resulting in eventual termination of viral DNA elongation.
Antiviral Activity: The median concentration of ganciclovir that inhibits CMV replication (IC_{50}) in vitro (laboratory strains or clinical isolates) has ranged from 0.02 to 3.48 µg/mL. Ganciclovir inhibits mammalian cell proliferation (CIC_{50}) in vitro at higher concentrations ranging from 30 to 725 µg/mL. Bone marrow-derived colony-forming cells are more sensitive (CIC_{50} 0.028 to 0.7 µg/mL). The relationship of in vitro sensitivity of CMV to ganciclovir and clinical response has not been established.
Clinical Antiviral Effect of CYTOVENE-IV and CYTOVENE Capsules: *CYTOVENE-IV:* In a study of CYTOVENE-IV treatment of life- or sight-threatening CMV disease in immunocompromised patients, 121 of 314 patients had CMV cultured within 7 days prior to treatment and sequential posttreatment viral cultures of urine, blood, throat and/or semen. As judged by conversion to culture negativity, or a greater than 100-fold decrease in in vitro CMV titer, at least 83% of patients had a virologic response with a median response time of 7 to 15 days.
Antiviral activity of CYTOVENE-IV was demonstrated in two randomized studies for the prevention of CMV disease in transplant recipients (see table below).
[See table below]
CYTOVENE Capsules: In trials comparing CYTOVENE-IV with CYTOVENE capsules for the maintenance treatment of CMV retinitis in patients with AIDS, serial urine cultures and other available cultures (semen, biopsy specimens, blood and others) showed that a small proportion of patients remained culture-positive during maintenance therapy with no statistically significant differences in CMV isolation rates between treatment groups.
A study of CYTOVENE capsules (1000 mg q8h) for prevention of CMV disease in individuals with advanced HIV infection (ICM 1654) evaluated antiviral activity as measured by CMV isolation in culture; most cultures were from urine. At baseline, 40% (176/436) and 44% (92/210) of ganciclovir and placebo recipients, respectively, had positive cultures (urine or blood). After 2 months on treatment, 10% vs 44% of ganciclovir vs placebo recipients had positive cultures.
Viral Resistance: The current working definition of CMV resistance to ganciclovir in in vitro assays is IC_{50} >3.0 µg/mL (12.0 µM). CMV resistance to ganciclovir has been observed in individuals with AIDS and CMV retinitis who have never received ganciclovir therapy. Viral resistance has also been observed in patients receiving prolonged treatment for CMV retinitis with CYTOVENE-IV. In a controlled study of oral ganciclovir for prevention of AIDS-associated CMV disease, 364 individuals had one or more cultures performed after at least 90 days of ganciclovir treatment. Of these, 113 had at least one positive culture. The last available isolate from each subject was tested for reduced sensitivity, and 2 of 40 were found to be resistant to ganciclovir. These resistant isolates were associated with subsequent treatment failure for retinitis.
The possibility of viral resistance should be considered in patients who show poor clinical response or experience persistent viral excretion during therapy. The principal mechanism of resistance to ganciclovir in CMV is the decreased ability to form the active triphosphate moiety; resistant viruses have been described that contain mutations in the UL97 gene of CMV that controls phosphorylation of ganciclovir. Mutations in the viral DNA polymerase have also been reported to confer viral resistance to ganciclovir.

Patients With Positive CMV Cultures

	Heart Allograft* (n=147)		Bone Marrow Allograft (n=72)	
Time	CYTOVENE-IV†	Placebo	CYTOVENE-IV‡	Placebo
Pretreatment	1/67 (2%)	5/64 (8%)	37/37 (100%)	35/35 (100%)
Week 2	2/75 (3%)	11/67 (16%)	2/31 (6%)	19/28 (68%)
Week 4	3/66 (5%)	28/66 (43%)	0/24 (0%)	16/20 (80%)

* CMV seropositive or receiving graft from seropositive donor
† 5 mg/kg bid for 14 days followed by 6 mg/kg qd for 5 days/week for 14 days
‡ 5 mg/kg bid for 7 days followed by 5 mg/kg qd until day 100 posttransplant

CLINICAL PHARMACOLOGY

Pharmacokinetics:

BECAUSE THE MAJOR ELIMINATION PATHWAY FOR GANCICLOVIR IS RENAL, DOSAGE REDUCTIONS ACCORDING TO CREATININE CLEARANCE ARE REQUIRED FOR CYTOVENE-IV AND SHOULD BE CONSIDERED FOR CYTOVENE CAPSULES. FOR DOSING INSTRUCTIONS IN PATIENTS WITH RENAL IMPAIRMENT, REFER TO DOSAGE AND ADMINISTRATION.

Absorption: The absolute bioavailability of oral ganciclovir under fasting conditions was approximately 5% (n=6) and following food was 6% to 9% (n=32). When ganciclovir was administered orally with food at a total daily dosage of 3 g/day (500 mg q3h, 6 times daily and 1000 mg tid), the steady-state absorption as measured by area under the serum concentration vs time curve (AUC) over 24 hours and maximum serum concentrations (C_{max}) were similar following both regimens with an AUC_{0-24} of 15.9 ± 4.2 (mean ± SD) and 15.4 ± 4.3 µg·hr/mL and C_{max} of 1.02 ± 0.24 and 1.18 ± 0.36 µg/mL, respectively (n=16).
At the end of a 1-hour intravenous infusion of 5 mg/kg ganciclovir, total AUC ranged between 22.1 ± 3.2 (n=16) and 26.8 ± 6.1 µg·hr/mL (n=16) and C_{max} ranged between 8.27 ± 1.02 (n=16) and 9.0 ± 1.4 µg/mL (n=16).
Food Effects: When CYTOVENE capsules were given with a meal containing 602 calories and 46.5% fat at a dosage of 1000 mg every 8 hours to 20 HIV-positive subjects, the steady-state AUC increased by 22 ± 22% (range: -6% to 68%) and there was a significant prolongation of time to peak serum concentrations (T_{max}) from 1.8 ± 0.8 to 3.0 ± 0.6 hours and a higher C_{max} (0.85 ± 0.25 vs 0.96 ± 0.27 µg/mL) (n=20).
Distribution: The steady-state volume of distribution of ganciclovir after intravenous administration was 0.74 ± 0.15 L/kg (n=98). For CYTOVENE capsules, no correlation was observed between AUC and reciprocal weight (range: 55 to 128 kg); oral dosing according to weight is not required. Cerebrospinal fluid concentrations obtained 0.25 to 5.67 hours postdose in 3 patients who received 2.5 mg/kg ganciclovir intravenously q8h or q12h ranged from 0.31 to 0.68 µg/mL representing 24% to 70% of the respective plasma concentrations. Binding to plasma proteins was 1% to 2% over ganciclovir concentrations of 0.5 and 51 µg/mL.
Metabolism: Following oral administration of a single 1000 mg dose of ^{14}C-labeled ganciclovir, 86 ± 3% of the administered dose was recovered in the feces and 5 ± 1% was recovered in the urine (n=4). No metabolite accounted for more than 1% to 2% of the radioactivity recovered in urine or feces.
Elimination: When administered intravenously, ganciclovir exhibits linear pharmacokinetics over the range of 1.6 to 5.0 mg/kg and when administered orally, it exhibits linear kinetics up to a total daily dose of 4 g/day. Renal excretion of unchanged drug by glomerular filtration and active tubular secretion is the major route of elimination of ganciclovir. In patients with normal renal function, 91.3 ± 5.0% (n=4) of intravenously administered ganciclovir was recovered unmetabolized in the urine. Systemic clearance of intravenously administered ganciclovir was 3.52 ± 0.80 mL/min/kg (n=98) while renal clearance was 3.20 ± 0.80 mL/min/kg (n=47), accounting for 91 ± 11% of the systemic clearance (n=47). After oral administration of ganciclovir, steady-state is achieved within 24 hours. Renal clearance following oral administration was 3.1 ± 1.2 mL/min/kg (n=22). Half-life was 3.5 ± 0.9 hours (n=98) following IV administration and 4.8 ± 0.9 hours (n=39) following oral administration.
Special Populations: *Renal Impairment:* The pharmacokinetics following intravenous administration of CYTOVENE-IV solution were evaluated in 10 immunocompromised patients with renal impairment who received doses ranging from 1.25 to 5.0 mg/kg.
[See first table at top of next page]
The pharmacokinetics of ganciclovir following oral administration of CYTOVENE capsules were evaluated in 44 patients, who were either solid organ transplant recipients or HIV positive. Apparent oral clearance of ganciclovir decreased and AUC_{0-24h} increased with diminishing renal function (as expressed by creatinine clearance). Based on these observations, it is necessary to modify the dosage of ganciclovir in patients with renal impairment (see DOSAGE AND ADMINISTRATION).
Hemodialysis reduces plasma concentrations of ganciclovir by about 50% after both intravenous and oral administration.
Race/Ethnicity and Gender: The effects of race/ethnicity and gender were studied in subjects receiving a dose regimen of 1000 mg every 8 hours. Although the numbers of blacks (16%) and Hispanics (20%) were small, there appeared to be a trend towards a lower steady-state C_{max} and

Thyrogen—Cont.

Geriatric Use
Results from controlled trials indicate no difference in the safety and efficacy of Thyrogen between adult patients less than 65 years and those greater than 65 years of age.

ADVERSE REACTIONS
Adverse reaction data are derived from the two clinical trials in which 381 patients were treated with Thyrogen (thyrotropin alfa for injection) and from post-marketing surveillance.
The most common adverse events (> 5%) reported in clinical trials were: nausea (10.5%) and headache (7.3%). Events reported in ≥ 1% of patients in the trials are summarized in the following table:

Summary of Adverse Events During Clinical Studies (≥ 1%)

	% of Patients with Adverse Events (n) (n = 381)
Body as a Whole	
Headache	7.3%(28)
Asthenia	3.4%(13)
Chills	1.0%(4)
Fever	1.0%(4)
Flu Syndrome	1.0%(4)
Digestive System	
Nausea	10.5%(40)
Vomiting	2.1%(8)
Nausea and Vomiting	1.3%(5)
Nervous System	
Dizziness	1.6%(6)
Paresthesia	1.6%(6)

There have been several reports of hypersensitivity reactions including urticaria, rash, pruritus, flushing and respiratory difficulties requiring treatment. However, in clinical trials no patients have developed antibodies to thyrotropin alfa, either after single dose or repeated (27 patients) use of the product.
Four patients out of 55 (7.3%) with CNS metastases who were followed in a special treatment protocol experienced acute hemiplegia, hemiparesis or pain one to three days after Thyrogen administration. The symptoms were attributed to local edema and/or focal hemorrhage at the site of the cerebral or spinal cord metastases. In addition, one case each of acute visual loss and of laryngeal edema with respiratory distress, requiring tracheotomy, with onset of symptoms within 24 hours after Thyrogen administration, have been reported in patients with metastases to the optic nerve and paratracheal areas, respectively. In addition, sudden, rapid and painful enlargement of locally recurring papillary carcinoma has been reported within 12-48 hours of Thyrogen administration. The enlargement was accompanied by dyspnea, stridor or dysphonia. Rapid clinical improvement occurred following glucocorticoid therapy. It is recommended that pretreatment with glucocorticoids be considered for patients in whom local tumor expansion may compromise vital anatomic structures.
A 77 year-old non-thyroidectomized patient with a history of heart disease and spinal metastases who received 4 Thyrogen injections over 6 days in a special treatment protocol experienced a fatal MI 24 hours after he received the last Thyrogen injection. The event was likely related to Thyrogen-induced hyperthyroidism.

OVERDOSAGE
There has been no reported experience of overdose in humans. However, in clinical trials, three patients experienced symptoms after receiving Thyrogen doses higher than those recommended. Two patients had natusea after a 2.7 mg IM dose, and in one of these patients, the event was accompanied by weakness, dizziness and headache. Another patient experienced nausea, vomiting and hot flashes after a 3.6 mg IM dose.
In addition, one patient experienced symptoms after receiving Thyrogen intravenously. This patient received 0.3 mg Thyrogen as a single intravenous bolus and, 15 minutes later experienced severe nausea, vomiting, diaphoresis, hypotension (BP decreased from 115/66 mm Hg to 81/44 mm Hg) and tachycardia (pulse increased from 75 to 117 bpm).

DOSAGE AND ADMINISTRATION
Thyrogen 0.9 mg intramuscularly may be administered every 24 hours for two doses or every 72 hours for three doses. After reconstitution with 1.2 mL Sterile Water for Injection, a 1.0 mL solution (0.9 mg thyrotropin alfa) is administered by intramuscular injection to the buttock.
For radioiodine imaging, radioiodine administration should be given 24 hours following the final Thyrogen injection. Scanning should be performed 48 hours after radioiodine administration (72 hours after the final injection of Thyrogen).
The following parameters utilized in the second Phase 3 study are recommended for radioiodine scanning with Thyrogen:
- A diagnostic activity of 4 mCi (148 MBq) ^{131}I should be used.
- Whole body images should be acquired for a minimum of 30 minutes and/or should contain a minimum of 140,000 counts.
- Scanning times for single (spot) images of body regions should be 10-15 minutes or less if the minimum number of counts is reached sooner (i.e., 60,000 for a large field of view camera, 35,000 counts for a small field of view).

For serum Tg testing, the serum sample should be obtained 72 hours after the final injection of Thyrogen.

INSTRUCTIONS FOR USE
Thyrogen (thyrotropin alfa for injection) is for intramuscular injection to the buttock. The powder should be reconstituted immediately prior to use with 1.2 mL of sterile Water for Injection, USP. Each vial of Thyrogen and each vial of diluent, if provided, is intended for single use. Discard unused portion of the diluent.
Thyrogen should be stored at 2-8°C (36-46°F). Each vial, after reconstitution with 1.2 mL of the accompanying Sterile Water for Injection, USP, should be inspected visually for particulate matter or discoloration before use. Any vials exhibiting particulate matter or discoloration should not be used.
If necessary, the reconstituted solution can be stored for up to 24 hours at a temperature between 2°C and 8°C, while avoiding microbial contamination.
DO NOT USE Thyrogen after the expiration date on the vial. Protect from light.

HOW SUPPLIED
Thyrogen (thyrotropin alfa for injection) is supplied as a sterile, non-pyrogenic, lyophilized product. It is available either in a two-vial kit or a four-vial kit. The two-vial kit contains two 1.1 mg vials of Thyrogen® (thyrotropin alfa for injection). The four-vial kit contains two 1.1 mg vials of Thyrogen®, as well as two 10 mL vials of Sterile Water for Injection, USP.
NDC 58468-1849-4 (4-vial kit)
NDC 58468-0030-2 (2-vial kit)
Store at 2-8°C.

Rx ONLY
Thyrogen® (thyrotropin alfa for injection)
Genzyme Corporation
One Kendall Square
Cambridge, MA 02139
(800) 745-4447
genzyme
GENERAL
therapeutics

4728 (7/03)

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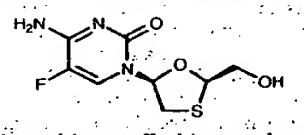
EMTRIVA™ ℞
[ĕm-trĭvă]
(emtricitabine)
Capsules
℞ Only

WARNING: LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION WITH OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION
EMTRIVA is the brand name of emtricitabine, a synthetic nucleoside analogue with activity against human immunodeficiency virus type 1 (HIV-1) reverse transcriptase.
The chemical name of emtricitabine is 5-fluoro-1-(2*R*,5*S*)-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. Emtricitabine is the (-) enantiomer of a thio analogue of cytidine, which differs from other cytidine analogues in that it has a fluorine in the 5-position.
It has a molecular formula of $C_8H_{10}FN_3O_3S$ and a molecular weight of 247.24. It has the following structural formula:

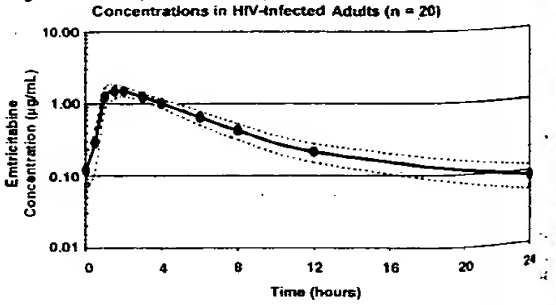


Emtricitabine is a white to off-white powder with a solubility of approximately 112 mg/mL in water at 25 °C. The log P for emtricitabine is –0.43 and the pKa is 2.65.
EMTRIVA capsules are for oral administration. Each capsule contains 200 mg of emtricitabine and the inactive ingredients, crospovidone, magnesium stearate, microcrystalline cellulose and povidone.

MICROBIOLOGY
Mechanism of Action:
Emtricitabine, a synthetic nucleoside analog of cytosine, is phosphorylated by cellular enzymes to form emtricitabine 5'-triphosphate. Emtricitabine 5'-triphosphate inhibits the activity of the HIV-1 reverse transcriptase by competing with the natural substrate deoxycytidine 5'-triphosphate and by being incorporated into nascent viral DNA which results in chain termination. Emtricitabine 5'-triphosphate is a weak inhibitor of mammalian DNA polymerase α, β, ε and mitochondrial DNA polymerase γ.
Antiviral Activity In Vitro:
The *in vitro* antiviral activity of emtricitabine against laboratory and clinical isolates of HIV was assessed in lymphoblastoid cell lines, the MAGI-CCR5 cell line, and peripheral blood mononuclear cells. The 50% inhibitory concentration (IC_{50}) value for emtricitabine was in the range of 0.0013 to 0.64 μM (0.0003 to 0.158 μg/mL). In drug combination studies of emtricitabine with nucleoside reverse transcriptase inhibitors (abacavir, lamivudine, stavudine, tenofovir, zalcitabine, zidovudine), non-nucleoside reverse transcriptase inhibitors (delavirdine, efavirenz, nevirapine), and protease inhibitors (amprenavir, nelfinavir, ritonavir, saquinavir), additive to synergistic effects were observed. Most of these drug combinations have not been studied in humans. Emtricitabine displayed antiviral activity *in vitro* against HIV-1 clades A, C, D, E, F, and G (IC_{50} values ranged from 0.007 to 0.075 μM) and showed strain specific activity against HIV-2 (IC_{50} values ranged from 0.007 to 1.5 μM).
Drug Resistance:
Emtricitabine-resistant isolates of HIV have been selected *in vitro*. Genotypic analysis of these isolates showed that the reduced susceptibility to emtricitabine was associated with a mutation in the HIV reverse transcriptase gene at codon 184 which resulted in an amino acid substitution of methionine by valine or isoleucine (M184V/I).
Emtricitabine-resistant isolates of HIV have been recovered from some patients treated with emtricitabine alone or in combination with other antiretroviral agents. In a clinical study, viral isolates from 37.5% of treatment-naïve patients with virologic failure showed reduced susceptibility to emtricitabine. Genotypic analysis of these isolates showed that the resistance was due to M184V/I mutations in the HIV reverse transcriptase gene.
Cross Resistance:
Cross-resistance among certain nucleoside analogue reverse transcriptase inhibitors has been recognized. Emtricitabine-resistant isolates (M184V/I) were cross-resistant to lamivudine and zalcitabine but retained sensitivity to abacavir, didanosine, stavudine, tenofovir, zidovudine, and NNRTIs (delavirdine, efavirenz, and nevirapine). HIV-1 isolates containing the K65R mutation, selected *in vivo* by abacavir, didanosine, tenofovir, and zalcitabine, demonstrated reduced susceptibility to inhibition by emtricitabine. Viruses harboring mutations conferring reduced susceptibility to stavudine and zidovudine (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) or didanosine (L74V) remained sensitive to emtricitabine. HIV-1 containing the K103N mutation associated with resistance to NNRTIs was susceptible to emtricitabine.

CLINICAL PHARMACOLOGY
Pharmacodynamics:
The *in vivo* activity of emtricitabine was evaluated in two clinical trials in which 101 patients were administered 25 to 400 mg a day of EMTRIVA as monotherapy for 10 to 14 days. A dose-related antiviral effect was observed, with a median decrease from baseline in plasma HIV-1 RNA of 1.3 log_{10} at a dose of 25 mg QD and 1.7 log_{10} to 1.9 log_{10} at a dose of 200 mg QD or BID.
Pharmacokinetics:
The pharmacokinetics of emtricitabine were evaluated in healthy volunteers and HIV-infected individuals. Emtricitabine pharmacokinetics are similar between these populations.
Figure 1 shows the mean steady-state plasma emtricitabine concentration-time profile in 20 HIV-infected subjects receiving EMTRIVA.

Figure 1. Mean (± 95% CI) Steady-State Plasma Emtricitabine Concentrations in HIV-Infected Adults (n = 20)



Absorption: Emtricitabine is rapidly and extensively absorbed following oral administration with peak plasma concentrations occurring at 1 to 2 hours post-dose. Following multiple dose oral administration of EMTRIVA to 20 HIV-infected subjects, the (mean ± SD) steady-state plasma emtricitabine peak concentration (C_{max}) was 1.8 ± 0.7 μg/mL and the area-under the plasma concentration-time curve over a 24-hour dosing interval (AUC) was 10.0 ±

15;4:311(8):496-501. 13. Hauser P, Voet P, Simoen E, et al. Immunological properties of recombinant HBsAg produced in yeast. *Postgrad Med J* 1987;63(Suppl 2):83-91. 14. Bush LM, Moonsammy GI, Boscia JA. Evaluation of initiating a hepatitis B vaccination schedule with one vaccine and completing it with another. *Vaccine* 1991;9(11):807-809. 15. Gutay C, Prinsen H, Safary A, et al. Immunization of homosexual men with a recombinant-DNA vaccine against hepatitis B: Immunogenicity and protection. In: Zuckerman AJ, ed. *Viral hepatitis and liver disease.* New York, NY: Alan R Liss, Inc.; 1988:1057-1058. 16. Centers for Disease Control and Prevention. 1998 Guidelines for treatment of sexually transmitted diseases. *MMWR* 1998;47(RR-1):102. 17. Centers for Disease Control and Prevention. General Recommendations on Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR* 1994;43(RR-1):1-38. 18. Centers for Disease Control. National Childhood Vaccine Injury Act: Requirements for permanent vaccination records and for reporting of selected events after vaccination. *MMWR* 1988;37 (13):197-200. 19. Public Health Service. National Vaccine Injury Compensation Program: Revision of the vaccine injury table. *Federal Register* February 8, 1995;60(26):7694.

*Yeast-derived, Hepatitis B Vaccine, MSD.
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RECOMBIVAX HB is a registered trademark of Merck & Co.
SAFETYGLIDE is a trademark of Becton, Dickinson and Company.

August 2003/EB:L34
Shown in Product Identification Guide, page 315

EPIVIR® Tablets ℞
(lamivudine tablets)

EPIVIR® Oral Solution ℞
(lamivudine oral solution)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING LAMIVUDINE AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

EPIVIR TABLETS AND ORAL SOLUTION (USED TO TREAT HIV INFECTION) CONTAIN A HIGHER DOSE OF THE ACTIVE INGREDIENT (LAMIVUDINE) THAN EPIVIR-HBV® TABLETS AND ORAL SOLUTION (USED TO TREAT CHRONIC HEPATITIS B). PATIENTS WITH HIV INFECTION SHOULD RECEIVE ONLY DOSING FORMS APPROPRIATE FOR TREATMENT OF HIV (SEE WARNINGS AND PRECAUTIONS).

SEVERE ACUTE EXACERBATIONS OF HEPATITIS B HAVE BEEN REPORTED IN PATIENTS WHO ARE CO-INFECTED WITH HEPATITIS B VIRUS (HBV) AND HIV AND HAVE DISCONTINUED EPIVIR. HEPATIC FUNCTION SHOULD BE MONITORED CLOSELY WITH BOTH CLINICAL AND LABORATORY FOLLOW-UP FOR AT LEAST SEVERAL MONTHS IN PATIENTS WHO DISCONTINUE EPIVIR AND ARE CO-INFECTED WITH HIV AND HBV. IF APPROPRIATE, INITIATION OF ANTI-HEPATITIS B THERAPY MAY BE WARRANTED (SEE WARNINGS).

DESCRIPTION

EPIVIR (also known as 3TC) is a brand name for lamivudine, a synthetic nucleoside analogue with activity against human immunodeficiency virus-1 (HIV-1) and hepatitis B virus (HBV). The chemical name of lamivudine is (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one. Lamivudine is the (-)enantiomer of a dideoxy analogue of cytidine. Lamivudine has also been referred to as (-)2',3'-dideoxy, 3'-thiacytidine. It has a molecular formula of $C_8H_{11}N_3O_3S$ and a molecular weight of 229.3.

Lamivudine is a white to off-white crystalline solid with a solubility of approximately 70 mg/mL in water at 20°C.

EPIVIR Tablets are for oral administration. Each 150-mg film-coated tablet contains 150 mg of lamivudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

Each 300-mg film-coated tablet contains 300 mg of lamivudine and the inactive ingredients black iron oxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, sodium starch glycolate, and titanium dioxide.

EPIVIR Oral Solution is for oral administration. One milliliter (1 mL) of EPIVIR Oral Solution contains 10 mg of lamivudine (10 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben, propylene glycol, propylparaben, sodium citrate (dihydrate), and sucrose (200 mg).

MICROBIOLOGY

Mechanism of Action: Lamivudine is a synthetic nucleoside analogue. Intracellularly, lamivudine is phosphorylated to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). The principal mode of action of L-TP is the inhibition of HIV-1 reverse transcriptase (RT) via DNA chain termination after incorporation of the nucleoside analogue into viral DNA. L-TP is a weak inhibitor of mammalian DNA polymerases α and β, and mitochondrial DNA polymerase γ.

Antiviral Activity In Vitro: The in vitro activity of lamivudine against HIV-1 was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard susceptibility assays. IC_{50} values (50% inhibitory concentrations) were in the range of 2 nM to 15 μM. Lamivudine had anti-HIV-1 activity in all acute virus-cell infections tested. In HIV-1–infected MT-4 cells, lamivudine in combination with zidovudine at various ratios exhibited synergistic antiretroviral activity. The relationship between in vitro susceptibility of HIV-1 to lamivudine and the inhibition of HIV-1 replication in humans has not been established. Please see the EPIVIR-HBV package insert for information regarding the inhibitory activity of lamivudine against HBV.

Drug Resistance: Lamivudine-resistant variants of HIV-1 have been selected in vitro. Genotypic analysis showed that the resistance was due to a specific amino acid substitution in the HIV-1 reverse transcriptase at codon 184 changing the methionine residue to either isoleucine or valine.

HIV-1 strains resistant to both lamivudine and zidovudine have been isolated from patients. Susceptibility of clinical isolates to lamivudine and zidovudine was monitored in controlled clinical trials. In patients receiving lamivudine monotherapy or combination therapy with lamivudine plus zidovudine, HIV-1 isolates from most patients became phenotypically and genotypically resistant to lamivudine within 12 weeks. In some patients harboring zidovudine-resistant virus at baseline, phenotypic sensitivity to zidovudine was restored by 12 weeks of treatment with lamivudine and zidovudine. Combination therapy with lamivudine plus zidovudine delayed the emergence of mutations conferring resistance to zidovudine.

Mutations in the HBV polymerase YMDD motif have been associated with reduced susceptibility of HBV to lamivudine in vitro. In studies of non-HIV-infected patients with chronic hepatitis B, HBV isolates with YMDD mutations were detected in some patients who received lamivudine daily for 6 months or more, and were associated with evidence of diminished treatment response; similar HBV mutants have been reported in HIV-infected patients who received lamivudine-containing antiretroviral regimens in the presence of concurrent infection with hepatitis B virus (see PRECAUTIONS and EPIVIR-HBV package insert).

Cross-Resistance: Lamivudine-resistant HIV-1 mutants were cross-resistant to didanosine (ddI) and zalcitabine (ddC). In some patients treated with zidovudine plus didanosine or zalcitabine, isolates resistant to multiple reverse transcriptase inhibitors, including lamivudine, have emerged.

Genotypic and Phenotypic Analysis of On-Therapy HIV-1 Isolates From Patients With Virologic Failure (see INDICATIONS AND USAGE: Description of Clinical Studies): The clinical relevance of genotypic and phenotypic changes associated with lamivudine therapy has not been fully established.

Study EPV20001: Fifty-three of 554 (10%) patients enrolled in EPV20001 were identified as virological failures (plasma HIV-1 RNA level ≥400 copies/mL) by Week 48. Twenty-eight patients were randomized to the lamivudine once-daily treatment group and 25 to the lamivudine twice-daily treatment group. The median baseline plasma HIV-1 RNA levels of patients in the lamivudine once-daily group and lamivudine twice-daily group were 4.9 $\log_{10}$ copies/mL and 4.6 $\log_{10}$ copies/mL, respectively.

Genotypic analysis of on-therapy isolates from 22 patients identified as virologic failures in the lamivudine once-daily group showed that isolates from 0/22 patients contained treatment-emergent mutations associated with zidovudine resistance (M41L, D67N, K70R, L210W, T215Y/F, or K219Q/E), isolates from 10/22 patients contained treatment-emergent mutations associated with efavirenz resistance (L100I, K101E, K103N, V108I, or Y181C), and isolates from 8/22 patients contained a treatment-emergent lamivudine resistance-associated mutation (M184I or M184V).

Genotypic analysis of on-therapy isolates from patients (n = 22) in the lamivudine twice-daily treatment group showed that isolates from 1/22 patients contained treatment-emergent zidovudine resistance mutations, isolates from 7/22 contained treatment-emergent efavirenz resistance mutations, and isolates from 5/22 contained treatment-emergent lamivudine resistance mutations.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine once daily showed that isolates from 12/13 patients were susceptible to zidovudine; isolates from 8/13 patients exhibited a 25- to 295-fold decrease in susceptibility to efavirenz, and isolates from 7/13 patients showed an 85- to 299-fold decrease in susceptibility to lamivudine.

Phenotypic analysis of baseline-matched on-therapy HIV-1 isolates from patients (n = 13) receiving lamivudine twice daily showed that isolates from all 13 patients were susceptible to zidovudine; isolates from 3/13 patients exhibited a 21- to 342-fold decrease in susceptibility to efavirenz, and isolates from 4/13 patients exhibited a 29- to 159-fold decrease in susceptibility to lamivudine.

Study EPV40001: Fifty patients received zidovudine 300 mg twice daily plus abacavir 300 mg twice daily plus lamivudine 300 mg once daily and 50 patients received zidovudine 300 mg plus abacavir 300 mg plus lamivudine 150 mg all twice daily. The median baseline plasma HIV-1 RNA levels for patients in the 2 groups were 4.79 $\log_{10}$ copies/mL and 4.83 $\log_{10}$ copies/mL, respectively. Fourteen of 50 patients in the lamivudine once-daily treatment group and 9 of 50 patients in the lamivudine twice-daily group were identified as virologic failures.

Genotypic analysis of on-therapy HIV-1 isolates from patients (n = 9) in the lamivudine once-daily treatment group showed that isolates from 6 patients had abacavir and/or lamivudine resistance-associated mutation M184V alone. On-therapy isolates from patients (n = 6) receiving lamivudine twice daily showed that isolates from 2 patients had M184V alone, and isolates from 2 patients harbored the M184V mutation in combination with zidovudine resistance-associated mutations.

Phenotypic analysis of on-therapy isolates from patients (n = 6) receiving lamivudine once daily showed that HIV-1 isolates from 4 patients exhibited a 32- to 53-fold decrease in susceptibility to lamivudine. HIV-1 isolates from these 6 patients were susceptible to zidovudine.

Phenotypic analysis of on-therapy isolates from patients (n = 4) receiving lamivudine twice daily showed that HIV-1 isolates from 1 patient exhibited a 45-fold decrease in susceptibility to lamivudine and a 4.5-fold decrease in susceptibility to zidovudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The steady-state pharmacokinetic properties of the EPIVIR 300-mg tablet once daily for 7 days compared to the EPIVIR 150-mg tablet twice daily for 7 days were assessed in a crossover study in 60 healthy volunteers. EPIVIR 300 mg once daily resulted in lamivudine exposures that were similar to EPIVIR 150 mg twice daily with respect to plasma $AUC_{24,ss}$; however, $C_{max,ss}$ was 66% higher and the trough value was 53% lower compared to the 150-mg twice-daily regimen. Intracellular lamivudine triphosphate exposures in peripheral blood mononuclear cells were also similar with respect to $AUC_{24,ss}$ and $C_{max24,ss}$; however, trough values were lower compared to the 150-mg twice-daily regimen. Inter-subject variability was greater for intracellular lamivudine triphosphate concentrations versus lamivudine plasma trough concentrations. The clinical significance of observed differences for both plasma lamivudine concentrations and intracellular lamivudine triphosphate concentrations is not known.

The pharmacokinetic properties of lamivudine have been studied in asymptomatic, HIV-infected adult patients after administration of single intravenous (IV) doses ranging from 0.25 to 8 mg/kg, as well as single and multiple (twice-daily regimen) oral doses ranging from 0.25 to 10 mg/kg.

The pharmacokinetic properties of lamivudine have also been studied as single and multiple oral doses ranging from 5 mg to 600 mg/day administered to HBV-infected patients.

Absorption and Bioavailability: Lamivudine was rapidly absorbed after oral administration in HIV-infected patients. Absolute bioavailability in 12 adult patients was 86% ± 16% (mean ± SD) for the 150-mg tablet and 87% ± 13% for the oral solution. After oral administration of 2 mg/kg twice a day to 9 adults with HIV, the peak serum lamivudine concentration (C_{max}) was 1.5 ± 0.5 mcg/mL (mean ± SD). The area under the plasma concentration versus time curve (AUC) and C_{max} increased in proportion to oral dose over the range from 0.25 to 10 mg/kg.

An investigational 25-mg dosage form of lamivudine was administered orally to 12 asymptomatic, HIV-infected patients on 2 occasions, once in the fasted state and once with food (1,099 kcal, 75 grams fat, 34 grams protein, 72 grams carbohydrate). Absorption of lamivudine was slower in the fed state (T_{max}: 3.2 ± 1.3 hours) compared with the fasted state (T_{max}: 0.9 ± 0.3 hours). C_{max} in the fed state was 40% ± 23% (mean ± SD) lower than in the fasted state. There was no significant difference in systemic exposure (AUC_∞) in the fed and fasted states; therefore, EPIVIR Tablets and Oral Solution may be administered with or without food.

The accumulation ratio of lamivudine in HIV-positive asymptomatic adults with normal renal function was 1.50 following 15 days of oral administration of 2 mg/kg twice daily.

Distribution: The apparent volume of distribution after IV administration of lamivudine to 20 patients was 1.3 ± 0.4 L/kg, suggesting that lamivudine distributes into extravascular spaces. Volume of distribution was independent of dose and did not correlate with body weight.

Binding of lamivudine to human plasma proteins is low (<36%). In vitro studies showed that, over the concentra-

Continued on next page

Product information on these pages is effective as of August 2004. Further information is available at GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

Vascular (extracardiac) Disorders: *Infrequent:* Hemorrhoids, peripheral ischemia, pulmonary embolism, thrombosis, thrombophlebitis deep, aneurysm, hemorrhage intracranial.
Vision Disorders: *Frequent:* Cataract. *Infrequent:* Conjunctival hemorrhage, blepharitis, diplopia, eye pain, glaucoma.
White Cell and Resistance Disorders: *Infrequent:* Lymphadenopathy, leukocytosis.
Post-Introduction Reports
Voluntary reports of adverse events temporally associated with Exelon that have been received since market introduction that are not listed above, and that may or may not be causally related to the drug include the following:
Skin and Appendages: Stevens-Johnson syndrome.

OVERDOSAGE

Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.
As Exelon® (rivastigmine tartrate) has a short plasma half-life of about one hour and a moderate duration of acetylcholinesterase inhibition of 8-10 hours, it is recommended that in cases of asymptomatic overdoses, no further dose of Exelon should be administered for the next 24 hours.
As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Atypical responses in blood pressure and heart rate have been reported with other drugs that increase cholinergic activity when co-administered with quaternary anticholinergics such as glycopyrrolate. Due to the short half-life of Exelon, dialysis (hemodialysis, peritoneal dialysis, or hemofiltration) would not be clinically indicated in the event of an overdose.
In overdoses accompanied by severe nausea and vomiting, the use of antiemetics should be considered. In a documented case of a 46 mg overdose with Exelon, the patient experienced vomiting, incontinence, hypertension, psychomotor retardation, and loss of consciousness. The patient fully recovered within 24 hours and conservative management was all that was required for treatment.

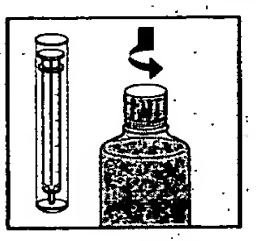
DOSAGE AND ADMINISTRATION

The dosage of Exelon® (rivastigmine tartrate) shown to be effective in controlled clinical trials is 6-12 mg/day, given as twice a day dosing (daily doses of 3 to 6 mg BID). There is evidence from the clinical trials that doses at the higher end of this range may be more beneficial.
The starting dose of Exelon is 1.5 mg twice a day (BID). If this dose is well tolerated, after a minimum of two weeks of treatment, the dose may be increased to 3 mg BID. Subsequent increases to 4.5 mg BID and 6 mg BID should be attempted after a minimum of 2 weeks at the previous dose. If adverse effects (e.g., nausea, vomiting, abdominal pain, loss of appetite) cause intolerance during treatment, the patient should be instructed to discontinue treatment for several doses and then restart at the same or next lower dose level. If treatment is interrupted for longer than several days, treatment should be reinitiated with the lowest daily dose and titrated as described above *(see WARNINGS)*. The maximum dose is 6 mg BID (12 mg/day).
Exelon should be taken with meals in divided doses in the morning and evening.
Recommendations for Administration: Caregivers should be instructed in the correct procedure for administering Exelon Oral Solution. In addition, they should be directed to the Instruction Sheet (included with the product) describing how the solution is to be administered. Caregivers should direct questions about the administration of the solution to either their physician or pharmacist *(see PRECAUTIONS: Information for Patients and Caregivers)*.
Patients should be instructed to remove the oral dosing syringe provided in its protective case, and using the provided syringe, withdraw the prescribed amount of Exelon Oral Solution from the container. Each dose of Exelon Oral Solution may be swallowed directly from the syringe or first mixed with a small glass of water, cold fruit juice or soda. Patients should be instructed to stir and drink the mixture.
Exelon Oral Solution and Exelon Capsules may be interchanged at equal doses.

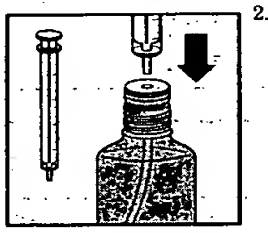
HOW SUPPLIED

Exelon® (rivastigmine tartrate) Oral Solution is supplied as 120 mL of a clear, yellow solution (2 mg/mL base) in a 4 ounce USP Type III amber glass bottle with a child-resistant 28 mm cap, 0.5 mm foam liner, dip tube and self-aligning plug. The oral solution is packaged with a dispenser set which consists of an assembled oral dosing syringe that allows dispensing a maximum volume of 3 mL corresponding to a 6 mg dose, with a plastic tube container.
Bottles of 120 mL ..... NDC 0078-0339-31
Store below 77°F (25°C) in an upright position and protect from freezing.
When Exelon Oral Solution is combined with cold fruit juice or soda, the mixture is stable at room temperature for up to 4 hours.

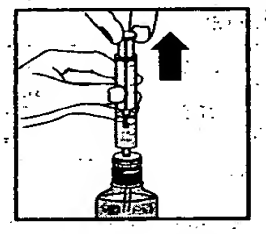
Exelon® (rivastigmine tartrate) Oral Solution
Instructions for Use



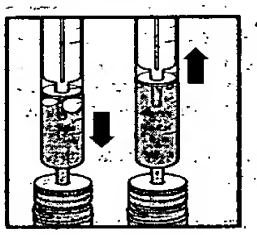
1. Remove oral dosing syringe from its protective case.
Push down and twist child resistant closure to open bottle.



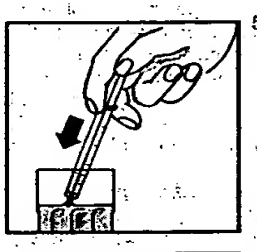
2. Insert tip of syringe into opening of white stopper.



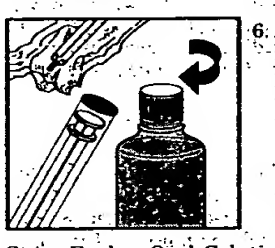
3. While holding the syringe, pull the plunger up to the level (see markings on side of syringe) that equals the dose prescribed by your doctor.



4. Before removing syringe containing prescribed dose from bottle, push out large bubbles by moving plunger up and down a few times. After the large bubbles are gone, pull the plunger again to the level that equals the dose prescribed by your doctor. Do not worry about a few tiny bubbles. This will not affect your dose in any way.
Remove the syringe from the bottle.



5. You may swallow Exelon Oral Solution directly from the syringe or mix with a small glass of water, cold fruit juice or soda. If mixing with water, juice or soda, be sure to stir completely and to drink the entire mixture. DO NOT MIX WITH OTHER LIQUIDS.



6. After use, wipe outside of syringe with a clean tissue and put it back into its case.
Close bottle using child resistant closure.

Store Exelon Oral Solution at room temperature (below 77°F) in an upright position. Do not place in freezer.
(86000501 4/00)
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Lincoln, Nebraska 68517
Distributed by:
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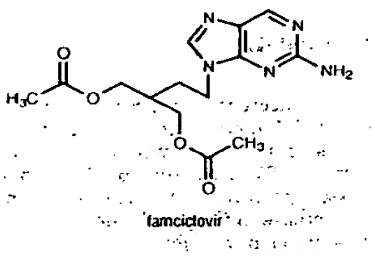
East Hanover, New Jersey 07936

FAMVIR® Rx
[fam-vir]
(famciclovir)
Tablets
Rx only

Prescribing Information
The following prescribing information is based on official labeling in effect July 2004.

DESCRIPTION

Famvir® (famciclovir) contains famciclovir, an orally administered prodrug of the antiviral agent penciclovir. Chemically, famciclovir is known as 2-[2-(2-amino-9*H*-purin-9-yl)ethyl]-1,3-propanediol diacetate. Its molecular formula is $C_{14}H_{19}N_5O_4$; its molecular weight is 321.3. It is a synthetic acyclic guanine derivative and has the following structure
[See chemical structure at top of next column]
Famciclovir is a white to pale yellow solid. It is freely soluble in acetone and methanol, and sparingly soluble in ethanol and isopropanol. At 25°C famciclovir is freely soluble (>25% w/v) in water initially, but rapidly precipitates as the



sparingly soluble (2%-3% w/v) monohydrate. Famciclovir is not hygroscopic below 85% relative humidity. Partition coefficients are: octanol/water (pH 4.8) P=1:09 and octanol/phosphate buffer (pH 7.4) P=2.08.
Tablets for Oral Administration: Each white, film-coated tablet contains famciclovir. The 125-mg and 250-mg tablets are round; the 500-mg tablets are oval. Inactive ingredients consist of hydroxypropyl cellulose, hydroxypropyl methylcellulose, lactose, magnesium stearate, polyethylene glycols, sodium starch glycolate and titanium dioxide.

MICROBIOLOGY

Mechanism of Antiviral Activity: Famciclovir undergoes rapid biotransformation to the active antiviral compound penciclovir, which has inhibitory activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella zoster virus (VZV). In cells infected with HSV-1, HSV-2 or VZV, viral thymidine kinase phosphorylates penciclovir to a monophosphate form that, in turn, is converted to penciclovir triphosphate by cellular kinases. *In vitro* studies demonstrate that penciclovir triphosphate inhibits HSV-2 DNA polymerase competitively with deoxyguanosine triphosphate. Consequently, herpes viral DNA synthesis and, therefore, replication are selectively inhibited.
Penciclovir triphosphate has an intracellular half-life of 10 hours in HSV-1-, 20 hours in HSV-2- and 7 hours in VZV-infected cells cultured *in vitro*; however, the clinical significance is unknown.
Antiviral Activity *In Vitro* and *In Vivo*: In cell culture studies, penciclovir has antiviral activity against the following herpes viruses (listed in decreasing order of potency): HSV-1, HSV-2 and VZV. Sensitivity test results, expressed as the concentration of the drug required to inhibit the growth of the virus by 50% (IC_{50}) or 99% (IC_{99}) in cell culture, vary greatly depending upon a number of factors, including the assay protocols, and in particular the cell type used. *See Table 1.*
[See table 1 at top of next page]
Drug Resistance: Penciclovir-resistant mutants of HSV and VZV can result from mutations in the viral thymidine kinase (TK) and DNA polymerase genes. Mutations in the viral TK gene may lead to complete loss of TK activity (TK negative), reduced levels of TK activity (TK partial), or alteration in the ability of viral TK to phosphorylate the drug without an equivalent loss in the ability to phosphorylate thymidine (TK altered). The most commonly encountered acyclovir-resistant mutants that are TK negative are also resistant to penciclovir. The possibility of viral resistance to penciclovir should be considered in patients who fail to respond or experience recurrent viral shedding during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics
Absorption and Bioavailability: Famciclovir is the diacetyl 6-deoxy analog of the active antiviral compound penciclovir. Following oral administration, little or no famciclovir is detected in plasma or urine.
The absolute bioavailability of famciclovir is 77±8% as determined following the administration of a 500-mg famciclovir oral dose and a 400-mg penciclovir intravenous dose to 12 healthy male subjects.
Penciclovir concentrations increased in proportion to dose over a famciclovir dose range of 125 mg to 750 mg administered as a single dose. Single oral-dose administration of 125-mg, 250-mg or 500-mg famciclovir to healthy male volunteers across 17 studies gave the following pharmacokinetic parameters:

Table 2

Dose	$AUC_{(0\text{-}inf)}$† (mcg hr/mL)	C_{max}‡ (mcg/mL)	T_{max}§ (h)
125 mg	2.24	0.8	0.9
250 mg	4.48	1.6	0.9
500 mg	8.95	3.3	0.9

†$AUC_{(0\text{-}inf)}$ (mcg hr/mL)=area under the plasma concentration-time profile extrapolated to infinity.
‡C_{max} (mcg/mL)=maximum observed plasma concentration.
§T_{max} (h)=time to C_{max}.

Following single oral-dose administration of 500-mg famciclovir to seven patients with herpes zoster, the mean ± SD AUC, C_{max}, and T_{max} were 12.1±1.7 mcg hr/mL, 4.0±0.7 mcg/mL, and 0.7±0.2 hours, respectively. The AUC of penciclovir was approximately 35% greater in patients with herpes zoster as compared to healthy volunteers. Some of this difference may be due to differences in renal function between the two groups.
There is no accumulation of penciclovir after the administration of 500-mg famciclovir t.i.d. for 7 days.

Continued on next page

Fuzeon—Cont.

clear glass vial containing 108 mg of enfuvirtide for the delivery of approximately 90 mg/1 mL when reconstituted with 1.1 mL of Sterile Water for Injection.

FUZEON is available in a Convenience Kit containing 60 single-use vials (2 cartons of 30 each) of FUZEON (90 mg strength), 60 vials (2 cartons of 30 each) of Sterile Water for Injection (1.1 mL per vial), 60 reconstitution syringes (3 cc), 60 administration syringes (1 cc), alcohol wipes, Package Insert, Patient Package Insert, and Injection Instruction Guide (NDC 0004-0380-39).

Storage Conditions

Store at 25°C (77°F); excursions permitted to 15° to 30°C (59° to 86°F) [See USP Controlled Room Temperature].

Reconstituted solution should be stored under refrigeration at 2° to 8°C (36° to 46°F) and used within 24 hours.

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FUZEON has been jointly developed by Trimeris, Inc. and Hoffmann-La Roche Inc. FUZEON is manufactured by Hoffmann-La Roche Inc.

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Durham, North Carolina 27707
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Issued: March 2003

HIVID®

[hī-vĭd]
(zalcitabine)
TABLETS

WARNING:

THE USE OF HIVID HAS BEEN ASSOCIATED WITH SIGNIFICANT CLINICAL ADVERSE REACTIONS, SOME OF WHICH ARE POTENTIALLY FATAL. HIVID CAN CAUSE SEVERE PERIPHERAL NEUROPATHY AND BECAUSE OF THIS SHOULD BE USED WITH EXTREME CAUTION IN PATIENTS WITH PREEXISTING NEUROPATHY. HIVID MAY ALSO RARELY CAUSE PANCREATITIS AND PATIENTS WHO DEVELOP ANY SYMPTOMS SUGGESTIVE OF PANCREATITIS WHILE USING HIVID SHOULD HAVE THERAPY SUSPENDED IMMEDIATELY UNTIL THIS DIAGNOSIS IS EXCLUDED.

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF ANTIRETROVIRAL NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING HIVID (SEE WARNINGS).

IN ADDITION, RARE CASES OF HEPATIC FAILURE AND DEATH CONSIDERED POSSIBLY RELATED TO UNDERLYING HEPATITIS B AND HIVID HAVE BEEN REPORTED (SEE WARNINGS AND PRECAUTIONS).

DESCRIPTION

HIVID is the Hoffmann-La Roche brand of zalcitabine [formerly called 2',3'-dideoxycytidine (ddC)], a synthetic pyrimidine nucleoside analogue active against the human immunodeficiency virus (HIV). HIVID is available as film-coated tablets for oral administration in strengths of 0.375 mg and 0.750 mg. Each tablet also contains the inactive ingredients lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, and polysorbate 80 along with the following colorant system: 0.375 mg tablet — synthetic brown, black, red and yellow iron oxides, and titanium dioxide; 0.750 mg tablet — synthetic black iron oxide and titanium dioxide. The chemical name for zalcitabine is 4-amino-1-beta-D-2', 3'-dideoxyribofuranosyl-2-(1H)-pyrimidone or 2',3'-dideoxycytidine with the molecular formula $C_9H_{13}N_3O_3$ and a molecular weight of 211.22.

Zalcitabine is a white to off-white crystalline powder with an aqueous solubility of 76.4 mg/mL at 25°C.

MICROBIOLOGY

Mechanism of Action: Zalcitabine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxycytidine, in which the 3'-hydroxyl group is replaced by hydrogen. Within cells, zalcitabine is converted to the active metabolite, dideoxycytidine 5'-triphosphate (ddCTP), by the sequential action of cellular enzymes. Dideoxycytidine 5'-triphosphate inhibits the activity of the HIV-reverse transcriptase both by competing for utilization of the natural substrate, deoxycytidine 5'-triphosphate (dCTP), and by its incorporation into viral DNA. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite, ddCTP, is also an inhibitor of cellular DNA polymerase-beta and mitochondrial DNA polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zalcitabine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{95} values (50% and 95% inhibitory concentration) were in the range of 30 to 500 nM and 100 to 1000 nM, respectively (1 nM = 0.21 ng/mL). Zalcitabine showed antiviral activity in all acute infections; however, activity was substantially less in chronically infected cells. In drug combination studies with zidovudine (ZDV) or saquinavir, zalcitabine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse-transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with a reduction in sensitivity to zalcitabine (ddC) have been isolated from a small number of patients treated with HIVID by 1 year of therapy. Genetic analysis of these isolates showed point mutations (Lys 65 Arg or Asn, Thr 69 Asp, Leu 74 Val, Val 75 Thr or Ala, Met 184 Val or Tyr 215 Cys) in the pol gene that encodes for the reverse transcriptase. Combination therapy with HIVID and ZDV does not appear to prevent the emergence of zidovudine-resistant isolates.

Cross-resistance: The potential for cross-resistance between HIV-reverse transcriptase inhibitors and HIV-protease inhibitors is low because of the different enzyme targets involved. The point mutation at position 69 appears to be specific to ddC in its selection and effect. Additionally, the point mutations at positions 65, 74, 75, and 184 are associated with resistance to didanosine (ddI), that at position 75 with resistance to stavudine (d4T), and those at positions 65 (Lys to Arg), and 184 (Met to Val) with resistance to lamivudine (3TC). HIV isolates with multidrug resistance to ZDV, ddI, ddC, d4T, and 3TC were recovered from a small number of patients treated for 1 year with the combination of ZDV, ddI or ddC. The pattern of resistance mutations in the combination therapy was different (Ala 62 Val, Val 75 Ile, Phe 77 Leu, Phe 116 Tyr and Gln 151 Met) from monotherapy with mutation 151 being most significant for multidrug resistance.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of zalcitabine has been evaluated in studies in HIV-infected patients following 0.01 mg/kg, 0.03 mg/kg, and 1.5 mg oral doses, and a 1.5 mg intravenous dose administered as a 1-hour infusion.

Absorption and Bioavailability in Adults: Following oral administration to HIV-infected patients, the mean absolute bioavailability of zalcitabine was >80% (30% CV, range 23% to 124%, n=19). The absorption rate of a 1.5 mg oral dose of zalcitabine (n=20) was reduced when administered with food. This resulted in a 39% decrease in mean maximum plasma concentrations (C_{max}) from 25.2 ng/mL (35% CV, range 11.6 to 37.5 ng/mL) to 15.5 ng/mL (24% CV, range 9.1 to 23.7 ng/mL), and a twofold increase in time to achieve maximum plasma concentrations from a mean of 0.8 hours under fasting conditions to 1.6 hours when the drug was given with food. The extent of absorption (as reflected by AUC) was decreased by 14%, from 72 ng·hr/mL (28% CV, range 43 to 119 ng·hr/mL) to 62 ng·hr/mL (23% CV, range 42 to 91 ng·hr/mL). The clinical relevance of these decreases is unknown. Absorption of zalcitabine does not appear to be reduced in patients with diarrhea not caused by an identified pathogen.

Distribution in Adults: The steady-state volume of distribution following intravenous administration of a 1.5 mg dose of zalcitabine averaged 0.534 (± 0.127) L/kg (24% CV, range 0.304 to 0.734 L/kg, n=20). Cerebrospinal fluid obtained from 9 patients at 2 to 3.5 hours following 0.06 mg/kg or 0.09 mg/kg intravenous infusion showed measurable concentrations of zalcitabine. The CSF:plasma concentration ratio ranged from 9% to 37% (mean 20%), demonstrating penetration of the drug through the blood-brain barrier. The clinical relevance of these ratios has not been evaluated.

Metabolism and Elimination in Adults: Zalcitabine is phosphorylated intracellularly to zalcitabine triphosphate, the active substrate for HIV-reverse transcriptase. Concentrations of zalcitabine triphosphate are too low for quantitation following administration of therapeutic doses to humans.

Zalcitabine does not undergo a significant degree of metabolism by the liver. The primary metabolite of zalcitabine that has been identified is dideoxyuridine (ddU), which accounts for less than 15% of an oral dose in both urine and feces (n=4). Approximately 10% of an orally administered radiolabeled dose of zalcitabine appears in the feces (n=10), comprised primarily of unchanged drug and ddU. Renal excretion of unchanged drug appears to be the primary route of elimination, accounting for approximately 80% of an intravenous dose and 60% of an orally administered dose within 24 hours after dosing (n=19). The mean elimination half-life is 2 hours and generally ranges from 1 to 3 hours in individual patients. Total clearance following an intravenous dose averaged 285 mL/min (29% CV, range 165 to 447 mL/min, n=20). Renal clearance averaged approximately 235 mL/min, or about 80% of total clearance (30% CV, range 129 to 348 mL/min, n=20). Renal clearance exceeds glomerular filtration rate suggesting renal tubular secretion contributes to the elimination of zalcitabine by the kidneys.

In patients with impaired kidney function, prolonged elimination of zalcitabine may be expected. Preliminary results from 7 patients with renal impairment (estimated creatinine clearance <55 mL/min) indicate that the half-life was prolonged (up to 8.5 hours) in these patients compared to those with normal renal function. Maximum plasma concentrations were higher in some patients after a single dose (see PRECAUTIONS).

In patients with normal renal function, the pharmacokinetics of zalcitabine was not altered during 3 times daily multiple dosing (n=9). Accumulation of drug in plasma during this regimen was negligible. The drug was <4% bound to plasma proteins, indicating that drug interactions involving binding-site displacement are unlikely (see *Drug Interactions*).

Drug Interactions: *Zidovudine:* There was no significant pharmacokinetic interaction between zidovudine and zalcitabine when single doses of zalcitabine (1.5 mg) and zidovudine (200 mg) were coadministered to 12 HIV-positive patients.

Probenecid: Following administration of a single oral 1.5 mg dose of zalcitabine alone during probenecid treatment (500 mg at 8 and 2 hours before and 4 hours after zalcitabine dosing) to 12 HIV-positive patients, mean renal clearance decreased from 310 mL/min (28% CV) to 180 mL/min (22% CV) and AUC increased from 59 ng•hr/mL (27% CV) to 91 ng•hr/mL (22% CV), indicating an increase in exposure of approximately 50% to zalcitabine. Mean half-life of zalcitabine increased from 1.7 to 2.5 hours (see PRECAUTIONS).

Cimetidine: Administration of a single dose of 1.5 mg zalcitabine with a single dose of 800 mg cimetidine to 12 HIV-positive patients resulted in a decrease in renal clearance from 224 mL/min (27% CV) to 171 mL/min (39% CV) and an increase in AUC from 75 ng•hr/mL (29% CV) to 102 ng•hr/mL (35% CV) (see PRECAUTIONS) indicating an increase in exposure of approximately 36% to zalcitabine.

Maalox: Concomitant administration of Maalox® TC (30 mL) with single dose of 1.5 mg zalcitabine to 12 HIV-positive patients resulted in a decrease in mean C_{max} from 25.2 ng/mL (28% CV) to 18.4 ng/mL (34% CV) and AUC from 75 ng•hr/mL (29% CV, n=10) to 58 ng•hr/mL (36% CV, n=10) indicating a decrease in bioavailability of approximately 25% to zalcitabine (see PRECAUTIONS).

Metoclopramide: Administration of a single dose of 1.5 mg zalcitabine with 20 mg metoclopramide (10 mg 1 hour before and 10 mg 4 hours after zalcitabine dose) to 12 HIV-positive patients resulted in a decrease in AUC from 69 ng•hr/mL (16% CV) to 62 ng•hr/mL (21% CV) indicating a decrease in bioavailability of approximately 10% (see PRECAUTIONS).

Loperamide: Administration of a single dose of 1.5 mg zalcitabine during loperamide treatment (4 mg 16 hours before zalcitabine, 2 mg at 10 hours and 4 hours before zalcitabine, and 2 mg 2 hours after the zalcitabine dose) to 12 HIV-positive patients with diarrhea resulted in no significant pharmacokinetic interaction between zalcitabine and loperamide.

Pharmacokinetics in Pediatric Patients: For pharmacokinetic properties in pediatric patients, see PRECAUTIONS: *Pediatric Use.* Limited pharmacokinetic data have been reported for 5 HIV-positive pediatric patients using doses of 0.03 and 0.04 mg/kg HIVID administered orally every 6 hours.[1] The mean bioavailability of zalcitabine in these pediatric patients was 54% and mean apparent systemic clearance was 150 mL/min/m^2. Due to the small number of subjects and different analytical techniques, it is difficult to make comparisons between pediatric and adult data.

INDICATIONS AND USAGE

HIVID is indicated in combination with antiretroviral agents for the treatment of HIV infection. This indication is based on study results showing a reduction in the rate of disease progression (AIDS-defining events or death) in patients with limited prior antiretroviral therapy who were treated with the combination of HIVID and zidovudine (see *Description of Clinical Studies*). This indication is also based on a study showing a reduction in both mortality and AIDS-defining clinical events for patients who received INVIRASE® (saquinavir mesylate) in combination with HIVID compared to patients who received either HIVID or INVIRASE alone.

Description of Clinical Studies: The use of HIVID in combination with zidovudine is based on the clinical results from study ACTG 175. ACTG 175 was a randomized, double-blind, controlled trial that compared zidovudine 200 mg three times daily; didanosine 200 mg twice daily; zidovudine+didanosine; and zidovudine+HIVID 0.750 mg three times daily. A total of 2467 HIV-infected adults (mean baseline CD_4 count = 352 cells/mm^3) with no prior AIDS-defining event enrolled with the following demographics: male (82%), Caucasian (70%), mean age of 35 years, asymptomatic HIV infection (81%) and prior antiretroviral use (57%, mean duration = 89.5 weeks). The overall mean duration of study treatment was 99 weeks. The incidence of AIDS-defining events or death is shown in Table 1.

[See table 1 at bottom of next page]

Although no antiretroviral agent should be used as monotherapy, a description of CPCRA 002 is included here as it provides a comparison of the safety and efficacy of HIVID compared to ddI.

CPCRA 002 was a randomized, multicenter, open-label study in which HIVID was compared to ddI as treatment for patients with advanced HIV infection (median CD_4 cell count = 37 cells/mm^3) who were clinically intolerant to ZDV, or who had met criteria for having disease progression while receiving ZDV.[2] Patients in this study had a mean of

DESCRIPTION

RETROVIR is the brand name for zidovudine (formerly called azidothymidine [AZT]), a pyrimidine nucleoside analogue active against human immunodeficiency virus (HIV).

Tablets: RETROVIR Tablets are for oral administration. Each film-coated tablet contains 300 mg of zidovudine and the inactive ingredients hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, sodium starch glycolate, and titanium dioxide.

Capsules: RETROVIR Capsules are for oral administration. Each capsule contains 100 mg of zidovudine and the inactive ingredients corn starch, magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The 100-mg empty hard gelatin capsule, printed with edible black ink, consists of black iron oxide, dimethylpolysiloxane, gelatin, pharmaceutical shellac, soya lecithin, and titanium dioxide. The blue band around the capsule consists of gelatin and FD&C Blue No. 2.

Syrup: RETROVIR Syrup is for oral administration. Each teaspoonful (5 mL) of RETROVIR Syrup contains 50 mg of zidovudine and the inactive ingredients sodium benzoate 0.2% (added as a preservative), citric acid, flavors, glycerin, and liquid sucrose. Sodium hydroxide may be added to adjust pH.

The chemical name of zidovudine is 3′-azido-3′-deoxythymidine.

Zidovudine is a white to beige, odorless, crystalline solid with a molecular weight of 267.24 and a solubility of 20.1 mg/mL in water at 25°C. The molecular formula is $C_{10}H_{13}N_5O_4$.

MICROBIOLOGY

Mechanism of Action: Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido ($-N_3$) group. Within cells, zidovudine is converted to the active metabolite, zidovudine 5′-triphosphate (AztTP), by the sequential action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation and, therefore, the viral DNA growth is terminated. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.

In Vitro HIV Susceptibility: The in vitro anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC_{50} and IC_{90} values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC_{50} and IC_{90} values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively. Zidovudine showed antiviral activity in all acutely infected cell lines; however, activity was substantially less in chronically infected cell lines. In drug combination studies with zalcitabine, didanosine, lamivudine, saquinavir, indinavir, ritonavir, nevirapine, delavirdine, or interferon-alpha, zidovudine showed additive to synergistic activity in cell culture. The relationship between the in vitro susceptibility of HIV to reverse transcriptase inhibitors and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced sensitivity to zidovudine have been selected in vitro and were also recovered from patients treated with RETROVIR. Genetic analysis of the isolates showed mutations that result in 5 amino acid substitutions (Met41→Leu, A67→Asn, Lys70→Arg, Thr215→Tyr or Phe, and Lys219→Gln) in the viral reverse transcriptase. In general, higher levels of resistance were associated with greater number of mutations with 215 mutation being the most significant.

Cross-Resistance: The potential for cross-resistance between HIV reverse transcriptase inhibitors and protease inhibitors is low because of the different enzyme targets involved. Combination therapy with zidovudine plus zalcitabine or didanosine does not appear to prevent the emergence of zidovudine-resistant isolates. Combination therapy with RETROVIR plus EPIVIR® delayed the emergence of mutations conferring resistance to zidovudine. In some patients harboring zidovudine-resistant virus, combination therapy with RETROVIR plus EPIVIR restored phenotypic sensitivity to zidovudine by 12 weeks of treatment. HIV isolates with multidrug resistance to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine were recovered from a small number of patients treated for ≥1 year with the combination of zidovudine and didanosine or zalcitabine. The pattern of resistant mutations in the combination therapy was different (Ala62→Val, Val75→Ile, Phe77→116Tyr, and Gln→151Met) from monotherapy, with mutation 151 being most significant for multidrug resistance. Site-directed mutagenesis studies showed that these mutations could also result in resistance to zalcitabine, lamivudine, and stavudine.

CLINICAL PHARMACOLOGY

Pharmacokinetics: ***Adults:*** The pharmacokinetic properties of zidovudine in fasting patients are summarized in Table 1. Following oral administration, zidovudine is rapidly absorbed and extensively distributed, with peak serum concentrations occurring within 0.5 to 1.5 hours. Binding to plasma protein is low. Zidovudine is primarily eliminated by hepatic metabolism. The major metabolite of zidovudine is 3′-azido-3′-deoxy-5′-*O*-β-*D*-glucopyranuronosylthymidine (GZDV). GZDV area under the curve (AUC) is about 3-fold greater than the zidovudine AUC. Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration. A second metabolite, 3′-amino-3′-deoxythymidine (AMT), has been identified in the plasma following single-dose intravenous (IV) administration of zidovudine. The AMT AUC was one fifth of the zidovudine AUC. Pharmacokinetics of zidovudine were dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

The extent of absorption (AUC) was equivalent when zidovudine was administered as RETROVIR Tablets or Syrup compared to RETROVIR Capsules.

Table 1. Zidovudine Pharmacokinetic Parameters in Fasting Adult Patients

Parameter	Mean ± SD (except where noted)
Oral bioavailability (%)	64 ± 10 (n = 5)
Apparent volume of distribution (L/kg)	1.6 ± 0.6 (n = 8)
Plasma protein binding (%)	<38
CSF:plasma ratio*	0.6 [0.04 to 2.62] (n =39)
Systemic clearance (L/hr/kg)	1.6 ± 0.6 (n = 6)
Renal clearance (L/hr/kg)	0.34 ± 0.05 (n = 9)
Elimination half-life (hr)†	0.5 to 3 (n = 19)

*Median [range].
†Approximate range.

Adults with Impaired Renal Function: Zidovudine clearance was decreased resulting in increased zidovudine and GZDV half-life and AUC in patients with impaired renal function (n = 14) following a single 200-mg oral dose (Table 2). Plasma concentrations of AMT were not determined. A dose adjustment should not be necessary for patients with creatinine clearance (CrCl) ≥15 mL/min.

[See table 2 above]

The pharmacokinetics and tolerance of zidovudine were evaluated in a multiple-dose study in patients undergoing hemodialysis (n = 5) or peritoneal dialysis (n = 6) receiving escalating doses up to 200 mg 5 times daily for 8 weeks. Daily doses of 500 mg or less were well tolerated despite significantly elevated GZDV plasma concentrations. Apparent zidovudine oral clearance was approximately 50% of that reported in patients with normal renal function. Hemodialysis and peritoneal dialysis appeared to have a negligible effect on the removal of zidovudine, whereas GZDV elimination was enhanced. A dosage adjustment is recommended for patients undergoing hemodialysis or peritoneal dialysis (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Adults with Impaired Hepatic Function: Data describing the effect of hepatic impairment on the pharmacokinetics of zidovudine are limited. However, because zidovudine is eliminated primarily by hepatic metabolism, it is expected that zidovudine clearance would be decreased and plasma concentrations would be increased following administration of the recommended adult doses to patients with hepatic impairment (see DOSAGE AND ADMINISTRATION: Dose Adjustment).

Pediatrics: Zidovudine pharmacokinetics have been evaluated in HIV-infected pediatric patients (Table 3).

Patients from 3 Months to 12 Years of Age: Overall, zidovudine pharmacokinetics in pediatric patients greater than 3 months of age are similar to those in adult patients. Proportional increases in plasma zidovudine concentrations were observed following administration of oral solution from 90 to 240 mg/m^2 every 6 hours. Oral bioavailability, terminal half-life, and oral clearance were comparable to adult values. As in adult patients, the major route of elimination was by metabolism to GZDV. After intravenous dosing, about 29% of the dose was excreted in the urine unchanged, and about 45% of the dose was excreted as GZDV (see DOSAGE AND ADMINISTRATION: Pediatrics).

Table 2. Zidovudine Pharmacokinetic Parameters in Patients With Severe Renal Impairment*

Parameter	Control Subjects (Normal Renal Function) (n = 6)	Patients With Renal Impairment (n = 14)
CrCl (mL/min)	120 ± 8	18 ± 2
Zidovudine AUC (ng•hr/mL)	1,400 ± 200	3,100 ± 300
Zidovudine half-life (hr)	1.0 ± 0.2	1.4 ± 0.1

*Data are expressed as mean ± standard deviation.

Patients Younger Than 3 Months of Age: Zidovudine pharmacokinetics have been evaluated in pediatric patients from birth to 3 months of life. Zidovudine elimination was determined immediately following birth in 8 neonates who were exposed to zidovudine in utero. The half-life was 13.0 ± 5.8 hours. In neonates ≤14 days old, bioavailability was greater, total body clearance was slower, and half-life was longer than in pediatric patients >14 days old. For dose recommendations for neonates, see DOSAGE AND ADMINISTRATION: Neonatal Dosing.

[See table 3 at top of next page]

Pregnancy: Zidovudine pharmacokinetics have been studied in a Phase 1 study of 8 women during the last trimester of pregnancy. As pregnancy progressed, there was no evidence of drug accumulation. Zidovudine pharmacokinetics were similar to that of nonpregnant adults. Consistent with passive transmission of the drug across the placenta, zidovudine concentrations in neonatal plasma at birth were essentially equal to those in maternal plasma at delivery. Although data are limited, methadone maintenance therapy in 5 pregnant women did not appear to alter zidovudine pharmacokinetics. However, in another patient population, a potential for interaction has been identified (see PRECAUTIONS).

Nursing Mothers: **The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.** After administration of a single dose of 200 mg zidovudine to 13 HIV-infected women, the mean concentration of zidovudine was similar in human milk and serum (see PRECAUTIONS: Nursing Mothers).

Geriatric Patients: Zidovudine pharmacokinetics have not been studied in patients over 65 years of age.

Gender: A pharmacokinetic study in healthy male (n = 12) and female (n = 12) subjects showed no differences in zidovudine exposure (AUC) when a single dose of zidovudine was administered as the 300-mg RETROVIR Tablet.

Effect of Food on Absorption: RETROVIR may be administered with or without food. The extent of zidovudine absorption (AUC) was similar when a single dose of zidovudine was administered with food.

Drug Interactions: See Table 4 and PRECAUTIONS: Drug Interactions.

Zidovudine Plus Lamivudine: No clinically significant alterations in lamivudine or zidovudine pharmacokinetics were observed in 12 asymptomatic HIV-infected adult patients given a single dose of zidovudine (200 mg) in combination with multiple doses of lamivudine (300 mg every 12 hours).

[See table 4 at top of next page]

INDICATIONS AND USAGE

RETROVIR in combination with other antiretroviral agents is indicated for the treatment of HIV infection.

Maternal-Fetal HIV Transmission: RETROVIR is also indicated for the prevention of maternal-fetal HIV transmission as part of a regimen that includes oral RETROVIR beginning between 14 and 34 weeks of gestation, intravenous RETROVIR during labor, and administration of RETROVIR Syrup to the neonate after birth. The efficacy of this regimen for preventing HIV transmission in women who have received RETROVIR for a prolonged period before pregnancy has not been evaluated. The safety of RETROVIR for the mother or fetus during the first trimester of pregnancy has not been assessed (see Description of Clinical Studies).

Description of Clinical Studies: Therapy with RETROVIR has been shown to prolong survival and decrease the incidence of opportunistic infections in patients with advanced HIV disease and to delay disease progression in asymptomatic HIV-infected patients.

Combination Therapy in Adults: RETROVIR in combination with other antiretroviral agents has been shown to be superior to monotherapy for one or more of the following endpoints: delaying death, delaying development of AIDS, increasing CD4 cell counts, and decreasing plasma HIV RNA. The clinical efficacy of a combination regimen that includes RETROVIR was demonstrated in study ACTG320. This study was a multicenter, randomized, double-blind, placebo-controlled trial that compared RETROVIR 600 mg/day plus EPIVIR 300 mg/day to RETROVIR plus EPIVIR plus indinavir 800 mg t.i.d. The incidence of AIDS-defining events or death was lower in the triple-drug–containing

Continued on next page

Product information on these pages is effective as of August 2004. Further information is available at: GlaxoSmithKline, PO Box 13398, Research Triangle Park, NC 27709. 1-888-825-5249. Corporate Web Site: www.gsk.com

Tequin—Cont.

You should avoid TEQUIN if you have a rare condition known as congenital prolongation of the QTc interval. If any of your family members have this condition, you should inform your healthcare professional.
You should avoid TEQUIN if you are being treated for heart rhythm disturbances with certain medicines such as quinidine, procainamide, amiodarone, or sotalol. Inform your healthcare professional if you are taking a heart rhythm drug.
You should avoid TEQUIN if you have a condition known as hypokalemia (low blood potassium). Hypokalemia may be caused by medicines called diuretics such as furosemide and hydrochlorothiazide. If you are taking a diuretic you should speak with your healthcare professional.
If you are pregnant or planning to become pregnant while taking TEQUIN, talk to your doctor before taking this medication. TEQUIN is not recommended for use during pregnancy or nursing, as the effects on the unborn child or nursing infant are unknown.
TEQUIN is not recommended for children.

What about other medications I am taking?

It is important to let your healthcare provider know all of the medicines that you are using.

- It is important to let your healthcare provider know if you are taking certain medicines that can have an effect on an electrocardiogram test, such as cisapride, erythromycin, some antidepressants, and some antipsychotic drugs.
- You should tell your healthcare professional if you are taking medicines called diuretics (also sometimes called water pills) such as furosemide and hydrochlorothiazide, because diuretics can sometimes cause low potassium.
- If you have diabetes, it is important to let your healthcare provider know that you have this condition and what medications you are taking for it.
- Many antacids and multivitamins may interfere with the absorption of TEQUIN and may prevent it from working properly. You should take TEQUIN 4 hours before taking these products.

What are the possible side effects of TEQUIN?

TEQUIN (gatifloxacin) is generally well tolerated. The most common side effects that can occur while taking TEQUIN are usually mild and include nausea, vomiting, stomach pain, diarrhea, dizziness, and headache. You should be careful about driving or operating machinery until you are sure TEQUIN does not cause dizziness. If you notice any side effects not mentioned in this section or if you have any questions or concerns about the side effects you are experiencing, please discuss them with your healthcare professional.
In a few people, TEQUIN, like some other antibiotics, may produce a small effect on the heart that is seen on an electrocardiogram test. Although this has not caused any problems in more than 4000 patients who have taken TEQUIN in premarketing clinical trials, in theory, it could result in extremely rare cases of abnormal heartbeat, which may be dangerous. Contact your healthcare professional if you develop heart palpitations (fast beating) or have fainting spells.
Disturbances of blood sugar, including high blood sugar (hyperglycemia) and low blood sugar (hypoglycemia), have been reported with TEQUIN in diabetic patients. Elderly patients with additional medical problems or taking additional medications may also be at risk for high blood sugar. If you develop low blood sugar while on TEQUIN, you should take immediate measures to increase your blood sugar, stop taking TEQUIN, and contact your healthcare professional at once. If you develop high blood sugar while on TEQUIN, you should contact your healthcare professional at once before taking additional TEQUIN. If you have diabetes or suspect that you may have diabetes, discuss how to detect changes in your blood sugar with your healthcare professional at once before taking additional TEQUIN.

Where can I get more information about TEQUIN?

This section is a summary of the most important information about TEQUIN. It does not include everything there is to know about TEQUIN. If you have any questions or problems, you should talk to your doctor or healthcare provider. There is also a leaflet (Package Insert) written for healthcare professionals that your pharmacist can let you read. You may want to read this information and discuss it with your doctor or healthcare professional. Remember, no written information can replace careful discussion with your doctor.

Remember

- Take your dose of TEQUIN once a day.
- Complete the course of medication (take all of the pills) even if you are feeling better.
- Do not use TEQUIN for another condition or give it to others.
- Store TEQUIN tablets at room temperature in a tightly sealed container.
- Throw away TEQUIN when it is outdated or no longer needed by flushing it down the toilet.
- Keep this and all medications out of reach of children.

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Shown in Product Identification Guide, page 310

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(didanosine)
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VIDEX® EC (didanosine) Delayed-Release Capsules
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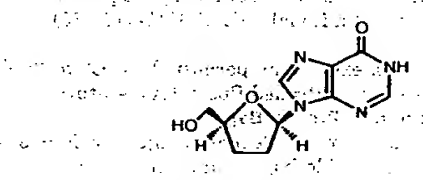
WARNING
FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WITH DIDANOSINE USED ALONE OR IN COMBINATION REGIMENS IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION. VIDEX EC SHOULD BE SUSPENDED IN PATIENTS WITH SUSPECTED PANCREATITIS AND DISCONTINUED IN PATIENTS WITH CONFIRMED PANCREATITIS (SEE WARNINGS).
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING DIDANOSINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF DIDANOSINE AND STAVUDINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF DIDANOSINE AND STAVUDINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

DESCRIPTION

VIDEX® EC (didanosine) is the brand name for an enteric-coated formulation of didanosine (ddI), a synthetic purine nucleoside analogue active against the Human Immunodeficiency Virus (HIV). VIDEX EC (didanosine) Delayed-Release Capsules, containing enteric-coated beadlets, are available for oral administration in strengths of 125, 200, 250, and 400 mg of didanosine. The inactive ingredients in the beadlets include carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, and talc. The capsule shells contain colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide. The capsules are imprinted with edible inks.
Didanosine is also available as buffered formulations. Please consult the prescribing information for VIDEX (didanosine) Chewable/Dispersible Buffered Tablets and Pediatric Powder for Oral Solution for additional information. The chemical name for didanosine is 2′,3′-dideoxyinosine. The structural formula is:



Didanosine is a white crystalline powder with the molecular formula $C_{10}H_{12}N_4O_3$ and a molecular weight of 236.2. The aqueous solubility of didanosine at 25°C and pH of approximately 6 is 27.3 mg/mL. Didanosine is unstable in acidic solutions. For example, at pH <3 and 37°C, 10% of didanosine decomposes to hypoxanthine in less than 2 minutes. In VIDEX EC (didanosine), an enteric coating is used to protect didanosine from degradation by stomach acid.

MICROBIOLOGY

Mechanism of Action: Didanosine is a synthetic nucleoside analogue of the naturally occurring nucleoside deoxyadenosine in which the 3′-hydroxyl group is replaced by hydrogen. Intracellularly, didanosine is converted by cellular enzymes to the active metabolite, dideoxyadenosine 5′-triphosphate. Dideoxyadenosine 5′-triphosphate inhibits the activity of HIV-1 reverse transcriptase both by competing with the natural substrate, deoxyadenosine 5′-triphosphate, and by its incorporation into viral DNA causing termination of viral DNA chain elongation.
***In Vitro* HIV Susceptibility:** The *in vitro* anti-HIV-1 activity of didanosine was evaluated in a variety of HIV-1 infected lymphoblastic cell lines and monocyte/macrophage cell cultures. The concentration of drug necessary to inhibit viral replication by 50% (IC_{50}) ranged from 2.5 to 10 μM (1 μM = 0.24 μg/mL) in lymphoblastic cell lines and 0.01 to 0.1 μM in monocyte/macrophage cell cultures. The relationship between *in vitro* susceptibility of HIV to didanosine and the inhibition of HIV replication in humans has not been established.
Drug Resistance: HIV-1 isolates with reduced sensitivity to didanosine have been selected *in vitro* and were also obtained from patients treated with didanosine. Genetic analysis of isolates from didanosine-treated patients showed mutations in the reverse transcriptase gene that resulted in the amino acid substitutions K65R, L74V, and M184V. The L74V mutation was most frequently observed in clinical isolates. Phenotypic analysis of HIV-1 isolates from 60 patients (some with prior zidovudine treatment) receiving 6 to 24 months of didanosine monotherapy showed that isolates from 10 of 60 patients exhibited an average of a 10-fold decrease in susceptibility to didanosine *in vitro* compared to baseline isolates. Clinical isolates that exhibited a decrease in didanosine susceptibility harbored one or more didanosine-associated mutations. The clinical relevance of genotypic and phenotypic changes associated with didanosine therapy has not been established.
Cross-resistance: HIV-1 isolates from 2 of 39 patients receiving combination therapy for up to 2 years with zidovudine and didanosine exhibited decreased susceptibility to zidovudine, didanosine, zalcitabine, stavudine, and lamivudine *in vitro* These isolates harbored five mutations (A62V, V75I, F77L, F116Y, and Q151M) in the reverse transcriptase gene. The clinical relevance of these observations has not been established.

CLINICAL PHARMACOLOGY

Animal Toxicology: Evidence of a dose-limiting skeletal muscle toxicity has been observed in mice and rats (but not in dogs) following long-term (greater than 90 days) dosing with didanosine at doses that were approximately 1.2 to 12 times the estimated human exposure. The relationship of this finding to the potential of didanosine to cause myopathy in humans is unclear. However, human myopathy has been associated with administration of didanosine and other nucleoside analogues.
Pharmacokinetics: The pharmacokinetic parameters of didanosine are summarized in Table 1. Didanosine is rapidly absorbed, with peak plasma concentrations generally observed from 0.25 to 1.50 hours following oral dosing with a buffered formulation. Increases in plasma didanosine concentrations were dose proportional over the range of 50 to 400 mg. Steady-state pharmacokinetic parameters did not differ significantly from values obtained after a single dose. Binding of didanosine to plasma proteins *in vitro* was low (<5%). Based on data from *in vitro* and animal studies, it is presumed that the metabolism of didanosine in man occurs by the same pathways responsible for the elimination of endogenous purines.

Table 1
Pharmacokinetic Parameters for Didanosine in Adults

Parameter	Mean ± SD	n
Oral bioavailability[a]	42±12%	6
Apparent volume of distribution[b]	1.08±0.22 L/kg	6

Table 2
Mean ± SD Pharmacokinetic Parameters for Didanosine Following a Single Oral Dose of a Buffered Formulation

	Creatinine Clearance (mL/min)				
Parameter	**≥ 90 (n=12)**	**60–90 (n=6)**	**30–59 (n=6)**	**10–29 (n=3)**	**Dialysis Patients (n=11)**
CL_{cr} (mL/min)	112±22	68±8	46±8	13±5	ND
CL/F (mL/min)	2164±638	1566±833	1023±378	628±104	543±174
CL_R (mL/min)	458±164	247±153	100±44	20±8	<10
$T_{1/2}$ (h)	1.42±0.33	1.59±0.13	1.75±0.43	2.0±0.3	4.1±1.2

ND = not determined due to anuria.
CL_{cr} = creatinine clearance.
CL/F = apparent oral clearance.
CL_R = renal clearance.

Store capsules in a tightly closed container at room temperature away from heat and out of the reach of children and pets.

If you have kidney disease: If your kidneys are not working properly, your doctor will need to do regular tests to check how they are working while you take VIDEX EC. Your doctor may also lower your dosage of VIDEX EC.

What should I do if someone takes an overdose of VIDEX EC?

If someone may have taken an overdose of VIDEX EC, get medical help right away. Contact their doctor or a poison control center.

What should I avoid while taking VIDEX EC?

Alcohol. Do not drink alcohol while taking VIDEX EC since alcohol may increase your risk of pancreatitis (pain and inflammation of the pancreas) or liver damage.

Other medicines. Other medicines, including those you can buy without a prescription, may interfere with the actions of VIDEX EC or may increase the possibility or severity of side effects. **Do not take any medicine, vitamin supplement, or other health preparation without first checking with your doctor.**

Pregnancy. It is not known if VIDEX EC can harm a human fetus. Also, pregnant women have experienced serious side effects when taking didanosine (the active ingredient in VIDEX EC (didanosine) in combination with ZERIT (stavudine), also known as d4T, and other HIV medicines. VIDEX EC should be used during pregnancy only after discussion with your doctor. **Tell your doctor if you become pregnant or plan to become pregnant while taking VIDEX EC.**

Nursing. Studies have shown didanosine (the active ingredient in VIDEX EC) is in the breast milk of animals getting the drug. It may also be in human breast milk. The Centers for Disease Control and Prevention (CDC) recommends that HIV-infected mothers **not** breast-feed. This should reduce the risk of passing HIV infection to their babies and the potential for serious adverse reactions in nursing infants. Therefore, do not nurse a baby while taking VIDEX EC.

What are the possible side effects of VIDEX EC?

Pancreatitis. Pancreatitis is a dangerous inflammation of the pancreas that may cause death. ***Tell your doctor right away if you develop stomach pain, nausea, or vomiting. These can be signs of pancreatitis.*** Before starting VIDEX EC therapy, let your doctor know if you have ever had pancreatitis. This condition is more likely to happen in people who have had it before. It is also more likely in people with advanced HIV disease. However, it can occur at any stage of HIV disease. It may be more common in patients with kidney problems, those who drink alcohol, and those who are also treated with stavudine or hydroxyurea. If you get pancreatitis, your doctor will tell you to stop taking VIDEX EC.

Lactic acidosis, severe liver enlargement, and **liver failure** including deaths, have been reported among patients taking VIDEX EC (including pregnant women). Symptoms that may indicate a liver problem are:

- feeling very weak, tired, or uncomfortable,
- unusual or unexpected stomach discomfort,
- feeling cold,
- feeling dizzy or lightheaded,
- suddenly developing a slow or irregular heartbeat.

Lactic acidosis is a medical emergency that must be treated in a hospital.

If you notice any of these symptoms or if your medical condition changes, stop taking VIDEX EC and **call your doctor right away** Women, overweight patients, and those who have been treated for a long time with other medicines used to treat HIV infection are more likely to develop lactic acidosis. Your doctor should check your liver function periodically while you are taking VIDEX EC. You should be especially careful if you have a history of heavy alcohol use or a liver problem.

Vision changes. VIDEX EC may affect the nerves in your eyes. Because of this, you should have regular eye examinations. You should also report any changes in vision to your doctor right away. This includes, for example, seeing colors abnormally or blurred vision.

Peripheral neuropathy. This is a problem with the nerves in your hands or feet. The nerve problem may be serious. ***Tell your doctor right away if you have continuing numbness, tingling, or pain in the feet or hands.***

Before starting VIDEX EC therapy, let your doctor know if you have ever had peripheral neuropathy. This condition is more likely to happen in people who have had it before. It is also more likely in patients taking medicines that affect the nerves and in people with advanced HIV disease. However, it can occur at any stage of HIV disease. If you get peripheral neuropathy, your doctor will tell you to stop taking VIDEX EC (didanosine). After stopping VIDEX EC, the symptoms may get worse for a short time and then get better. Once symptoms of peripheral neuropathy go away completely, you and your doctor should decide if starting VIDEX EC is right for you. If so, you might be started at a lower dose.

Special note about other medicines. If you take VIDEX EC along with other medicines with similar side effects, you may increase the chance of having these side effects. For example, using VIDEX EC in combination with other medicines that may cause pancreatitis, peripheral neuropathy, or liver problems (including stavudine and hydroxyurea) may increase your chance of having these side effects.

Other side effects: The most common side effects in adults taking VIDEX EC in combination with other HIV drugs included diarrhea, nausea, headache, vomiting, and rash. Changes in body fat have been seen in some patients taking antiretroviral therapy. These changes may include increased amount of fat in the upper back and neck ("buffalo hump"), breast, and around the trunk. Loss of fat from the legs, arms, and face may also happen. The cause and long-term health effects of these conditions are not known at this time.

Inactive Ingredients: Carboxymethylcellulose sodium 12, diethyl phthalate, methacrylic acid copolymer, sodium hydroxide, sodium starch glycolate, talc, colloidal silicon dioxide, gelatin, sodium lauryl sulfate, and titanium dioxide.

This medicine was prescribed for your particular condition. Do not use VIDEX EC for another condition or give it to others. Keep VIDEX EC and all medicines out of the reach of children. Throw away VIDEX EC when it is outdated or no longer needed by flushing it down the toilet or pouring it down the sink.

This summary does not include everything there is to know about VIDEX EC. Medicines are sometimes prescribed for purposes other than those listed in a Patient Information Leaflet. If you have questions or concerns, or want more information about VIDEX EC, your physician and pharmacist have the complete prescribing information upon which this leaflet is based. You may want to read it and discuss it with your doctor or other healthcare professional. Remember, no written summary can replace careful discussion with your doctor.

BMS Virology™
Bristol-Myers Squibb Company
Princeton, NJ 08543
U.S.A.

This Patient Information Leaflet has been approved by the U.S. Food and Drug Administration.

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F3-B0001-01-04 Revised January 2004
Based on Package Insert dated January 2004

Shown in Product Identification Guide, page 310

ZERIT® (stavudine) ℞
ZERIT® (stavudine) Capsules
ZERIT® (stavudine) for Oral Solution
(Patient Information Leaflet Included)

WARNING

LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING STAVUDINE AND OTHER ANTIRETROVIRALS. FATAL LACTIC ACIDOSIS HAS BEEN REPORTED IN PREGNANT WOMEN WHO RECEIVED THE COMBINATION OF STAVUDINE AND DIDANOSINE WITH OTHER ANTIRETROVIRAL AGENTS. THE COMBINATION OF STAVUDINE AND DIDANOSINE SHOULD BE USED WITH CAUTION DURING PREGNANCY AND IS RECOMMENDED ONLY IF THE POTENTIAL BENEFIT CLEARLY OUTWEIGHS THE POTENTIAL RISK (SEE WARNINGS AND PRECAUTIONS: PREGNANCY).

FATAL AND NONFATAL PANCREATITIS HAVE OCCURRED DURING THERAPY WHEN ZERIT (stavudine) WAS PART OF A COMBINATION REGIMEN THAT INCLUDED DIDANOSINE, WITH OR WITHOUT HYDROXYUREA,

IN BOTH TREATMENT-NAIVE AND TREATMENT-EXPERIENCED PATIENTS, REGARDLESS OF DEGREE OF IMMUNOSUPPRESSION (SEE WARNINGS).

DESCRIPTION

ZERIT® is the brand name for stavudine (d4T), a synthetic thymidine nucleoside analogue, active against the Human Immunodeficiency Virus (HIV).

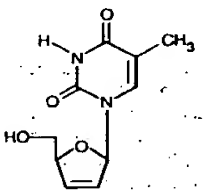
ZERIT (stavudine) Capsules are supplied for oral administration in strengths of 15, 20, 30, and 40 mg of stavudine. Each capsule also contains inactive ingredients microcrystalline cellulose, sodium starch glycolate, lactose, and magnesium stearate. The hard gelatin shell consists of gelatin, silicon dioxide, sodium lauryl sulfate, titanium dioxide, and iron oxides.

ZERIT (stavudine) for Oral Solution is supplied as a dye-free, fruit-flavored powder in bottles with child-resistant closures providing 200 mL of a 1 mg/mL stavudine solution upon constitution with water per label instructions. The powder for oral solution contains the following inactive ingredients: methylparaben, propylparaben, sodium carboxymethylcellulose, sucrose, and antifoaming and flavoring agents.

The chemical name for stavudine is 2′,3′-didehydro-3′-deoxythymidine. Stavudine has the following structural formula:

[See chemical structure at top of next column]

Stavudine is a white to off-white crystalline solid with the molecular formula $C_{10}H_{12}N_2O_4$ and a molecular weight of 224.2. The solubility of stavudine at 23°C is approximately 83 mg/mL in water and 30 mg/mL in propylene glycol. The n-octanol/water partition coefficient of stavudine at 23°C is 0.144.



MICROBIOLOGY

Mechanism of Action: Stavudine, a nucleoside analogue of thymidine, inhibits the replication of HIV in human cells *in vitro*. Stavudine is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV reverse transcriptase both by competing with the natural substrate deoxythymidine triphosphate (K_i=0.0083 to 0.032 μM), and by its incorporation into viral DNA causing a termination of DNA chain elongation because stavudine lacks the essential 3′-OH group. Stavudine triphosphate inhibits cellular DNA polymerase beta and gamma, and markedly reduces the synthesis of mitochondrial DNA.

***In vitro* HIV Susceptibility:** The *in vitro* antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit viral replication by 50% (ED_{50}) ranged from 0.009 to 4 μM against laboratory and clinical isolates of HIV-1. Stavudine had additive and synergistic activity in combination with didanosine and zalcitabine, respectively, *in vitro*. Stavudine combined with zidovudine had additive or antagonistic activity *in vitro* depending upon the molar ratios of the agents tested. The relationship between *in vitro* susceptibility of HIV to stavudine and the inhibition of HIV replication in humans has not been established.

Drug Resistance: HIV isolates with reduced susceptibility to stavudine have been selected *in vitro* and were also obtained from patients treated with stavudine. Phenotypic analysis of HIV isolates from stavudine-treated patients revealed, in 3 of 20 paired isolates, a 4- to 12-fold decrease in susceptibility to stavudine *in vitro*. The genetic basis for these susceptibility changes has not been identified. The clinical relevance of changes in stavudine susceptibility has not been established.

Cross-resistance: Five of 11 stavudine post-treatment isolates developed moderate resistance to zidovudine (9- to 176-fold) and 3 of those 11 isolates developed moderate resistance to didanosine (7- to 29-fold). The clinical relevance of these findings is unknown.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of stavudine have been evaluated in HIV-infected adult and pediatric patients (Tables 1 and 2). Peak plasma concentrations (C_{max}) and area under the plasma concentration-time curve (AUC) increased in proportion to dose after both single and multiple doses ranging from 0.03 to 4 mg/kg. There was no significant accumulation of stavudine with repeated administration every 6, 8, or 12 hours.

Absorption Following oral administration, stavudine is rapidly absorbed, with peak plasma concentrations occurring within 1 hour after dosing. The systemic exposure to stavudine is the same following administration as capsules or solution.

Distribution Binding of stavudine to serum proteins was negligible over the concentration range of 0.01 to 11.4 μg/mL. Stavudine distributes equally between red blood cells and plasma.

Metabolism The metabolic fate of stavudine has not been elucidated in humans.

Excretion Renal elimination accounted for about 40% of the overall clearance regardless of the route of administration. The mean renal clearance was about twice the average endogenous creatinine clearance, indicating active tubular secretion in addition to glomerular filtration.

[See table 1 at top of next page]

Special Populations:

Pediatric For pharmacokinetic properties of stavudine in pediatric patients, see Table 2.

[See table 2 on next page]

Renal Insufficiency Data from two studies in adults indicated that the apparent oral clearance of stavudine decreased and the terminal elimination half-life increased as creatinine clearance decreased (see Table 3). C_{max} and T_{max} were not significantly altered by renal insufficiency. The mean ± SD hemodialysis clearance value of stavudine was 120 ± 18 mL/min (n=12); the mean ± SD percentage of the stavudine dose recovered in the dialysate, timed to occur between 2-6 hours post-dose, was 31 ± 5%. Based on these observations, it is recommended that ZERIT (stavudine) dosage be modified in patients with reduced creatinine clearance and in patients receiving maintenance hemodialysis (see **DOSAGE AND ADMINISTRATION**).

[See table 3 on next page]

Hepatic Insufficiency Stavudine pharmacokinetics were not altered in 5 non-HIV-infected patients with hepatic impairment secondary to cirrhosis (Child-Pugh classification B or C) following the administration of a single 40-mg dose.

Geriatric Stavudine pharmacokinetics have not been studied in patients >65 years of age. (See **PRECAUTIONS: Geriatric Use.**)

Continued on next page

ZANTAC Syrup, a clear, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 mL (75 mg/5 mL) in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).
Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.
GlaxoSmithKline, Research Triangle Park, NC 27709
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April 2004/RL-2080
Shown in Product Identification Guide, page 318

ZIAGEN® ℞
[zi'ə-jin]
(abacavir sulfate)
Tablets

ZIAGEN® ℞
(abacavir sulfate)
Oral Solution

WARNING
FATAL HYPERSENSITIVITY REACTIONS HAVE BEEN ASSOCIATED WITH THERAPY WITH ZIAGEN. PATIENTS DEVELOPING SIGNS OR SYMPTOMS OF HYPERSENSITIVITY (WHICH INCLUDE FEVER; SKIN RASH; FATIGUE; GASTROINTESTINAL SYMPTOMS SUCH AS NAUSEA, VOMITING, DIARRHEA, OR ABDOMINAL PAIN; AND RESPIRATORY SYMPTOMS SUCH AS PHARYNGITIS, DYSPNEA, OR COUGH) SHOULD DISCONTINUE ZIAGEN AS SOON AS A HYPERSENSITIVITY REACTION IS SUSPECTED. TO AVOID A DELAY IN DIAGNOSIS AND MINIMIZE THE RISK OF A LIFE-THREATENING HYPERSENSITIVITY REACTION, ZIAGEN SHOULD BE PERMANENTLY DISCONTINUED IF HYPERSENSITIVITY CANNOT BE RULED OUT, EVEN WHEN OTHER DIAGNOSES ARE POSSIBLE (E.G., ACUTE ONSET RESPIRATORY DISEASES, GASTROENTERITIS, OR REACTIONS TO OTHER MEDICATIONS).
ZIAGEN SHOULD NOT BE RESTARTED FOLLOWING A HYPERSENSITIVITY REACTION BECAUSE MORE SEVERE SYMPTOMS WILL RECUR WITHIN HOURS AND MAY INCLUDE LIFE-THREATENING HYPOTENSION AND DEATH.
SEVERE OR FATAL HYPERSENSITIVITY REACTIONS CAN OCCUR WITHIN HOURS AFTER REINTRODUCTION OF ZIAGEN IN PATIENTS WHO HAVE NO IDENTIFIED HISTORY OR UNRECOGNIZED SYMPTOMS OF HYPERSENSITIVITY TO ABACAVIR THERAPY (SEE WARNINGS, PRECAUTIONS: INFORMATION FOR PATIENTS, AND ADVERSE REACTIONS).
LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY WITH STEATOSIS, INCLUDING FATAL CASES, HAVE BEEN REPORTED WITH THE USE OF NUCLEOSIDE ANALOGUES ALONE OR IN COMBINATION, INCLUDING ZIAGEN AND OTHER ANTIRETROVIRALS (SEE WARNINGS).

DESCRIPTION

ZIAGEN is the brand name for abacavir sulfate, a synthetic carbocyclic nucleoside analogue with inhibitory activity against HIV. The chemical name of abacavir sulfate is *(1S,cis)*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol sulfate (salt) (2:1). Abacavir sulfate is the enantiomer with *1S, 4R* absolute configuration on the cyclopentene ring. It has a molecular formula of $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$ and a molecular weight of 670.76 daltons.
Abacavir sulfate is a white to off-white solid with a solubility of approximately 77 mg/mL in distilled water at 25°C. It has an octanol/water (pH 7.1 to 7.3) partition coefficient (log *P*) of approximately 1.20 at 25°C.
ZIAGEN Tablets are for oral administration. Each tablet contains abacavir sulfate equivalent to 300 mg of abacavir and the inactive ingredients colloidal silicon dioxide; magnesium stearate, microcrystalline cellulose, and sodium starch glycolate. The tablets are coated with a film that is made of hypromellose, polysorbate 80, synthetic yellow iron oxide, titanium dioxide, and triacetin.
ZIAGEN Oral Solution is for oral administration. One milliliter (1 mL) of ZIAGEN Oral Solution contains abacavir sulfate equivalent to 20 mg of abacavir (20 mg/mL) in an aqueous solution and the inactive ingredients artificial strawberry and banana flavors, citric acid (anhydrous), methylparaben and propylparaben (added as preservatives), propylene glycol, saccharin sodium, sodium citrate (dihydrate), and sorbitol solution.
In vivo, abacavir sulfate dissociates to its free base, abacavir. In this insert, all dosages for ZIAGEN are expressed in terms of abacavir.

MICROBIOLOGY

Mechanism of Action: Abacavir is a carbocyclic synthetic nucleoside analogue. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5′-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. The lack of a 3′-OH group in the incorporated nucleoside analogue prevents the formation of the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated. Abacavir is a weak inhibitor of cellular DNA polymerases α, β, and γ.
Antiviral Activity: The in vitro anti-HIV-1 activity of abacavir was evaluated against a T-cell tropic laboratory strain HIV-1_{IIIB} in lymphoblastic cell lines, a monocyte/macrophage tropic laboratory strain HIV-1_{BaL} in primary monocytes/macrophages, and clinical isolates in peripheral blood mononuclear cells. The concentration of drug necessary to inhibit viral replication by 50 percent (IC_{50}) ranged from 3.7 to 5.8 μM against HIV-1_{IIIB}, and was 0.26 ± 0.18 μM (1 μM = 0.28 mcg/mL) against 8 clinical isolates. The IC_{50} value of abacavir against HIV-1_{BaL} varied from 0.07 to 1.0 μM. Abacavir had synergistic activity in vitro in combination with amprenavir, nevirapine, and zidovudine, and additive activity in combination with didanosine, lamivudine, stavudine, and zalcitabine.
Resistance: HIV-1 isolates with reduced sensitivity to abacavir have been selected in vitro and were also obtained from patients treated with abacavir. Genetic analysis of isolates from abacavir-treated patients showed point mutations in the reverse transcriptase gene that resulted in K65R, L74V, Y115F, and M184V amino acid substitutions. HIV-1 isolates from virologic failure antiretroviral-naive patients treated with abacavir alone (n = 67) contained the M184V mutation (n = 27), often in combination with the L74V mutation (n = 18). In some patients, the M184V mutation was also detected in combination with K65R and/or Y115F. Genetic analysis of isolates from virologic failure antiretroviral-naive patients treated with abacavir in combination with other antiretrovirals (n = 55) also showed that many isolates contained the M184V mutation (n = 26) alone, and, sometimes in combination with L74V (n = 2). In a clinical study of treatment-naive patients (CNA30024, n = 649) comparing ZIAGEN to zidovudine both in combination with efavirenz and lamivudine, 34 patients experienced virologic failure (plasma HIV-1 RNA >50 copies/mL, see CLINICAL STUDIES). Four patients in each treatment arm had viral isolates containing resistance-associated mutations including M184V and non-nucleoside reverse transcriptase inhibitor (NNRTI) mutations.
Cross-Resistance: Cross-resistance has been observed among nucleoside reverse transcriptase inhibitors. Recombinant laboratory strains of HIV-1_{HXB2} containing multiple abacavir resistance-associated mutations, namely, K65R, L74V, M184V, and Y115F, exhibited cross-resistance to didanosine, emtricitabine, lamivudine, tenofovir, and zalcitabine in vitro. The K65R mutation may also confer resistance to stavudine. An increasing number of thymidine analogue mutations (TAMs) (M41L, D67N, K70R, L210W, T215Y/F, K219E/R/H/Q/N) is associated with a progressive reduction in abacavir susceptibility.

CLINICAL PHARMACOLOGY

Pharmacokinetics in Adults: The pharmacokinetic properties of abacavir have been studied in asymptomatic, HIV-infected adult patients after administration of a single intravenous (IV) dose of 150 mg and after single and multiple oral doses. The pharmacokinetic properties of abacavir were independent of dose over the range of 300 to 1,200 mg/day.
Absorption and Bioavailability: Abacavir was rapidly and extensively absorbed after oral administration. The geometric mean absolute bioavailability of the tablet was 83%. After oral administration of 300 mg twice daily in 20 patients, the steady-state peak serum abacavir concentration (C_{max}) was 3.0 ± 0.89 mcg/mL (mean ± SD) and $AUC_{(0-12\ hr)}$ was 6.02 ± 1.73 mcg•hr/mL. Bioavailability of abacavir tablets was assessed in the fasting and fed states. There was no significant difference in systemic exposure (AUC_∞) in the fed and fasting states; therefore, ZIAGEN Tablets may be administered with or without food. Systemic exposure to abacavir was comparable after administration of ZIAGEN Oral Solution and ZIAGEN Tablets. Therefore, these products may be used interchangeably.
Distribution: The apparent volume of distribution after IV administration of abacavir was 0.86 ± 0.15 L/kg, suggesting that abacavir distributes into extravascular space. In 3 subjects, the CSF $AUC_{(0-6\ hr)}$ to plasma abacavir $AUC_{(0-6\ hr)}$ ratio ranged from 27% to 33%.
Binding of abacavir to human plasma proteins is approximately 50%. Binding of abacavir to plasma proteins was independent of concentration. Total blood and plasma drug-related radioactivity concentrations are identical, demonstrating that abacavir readily distributes into erythrocytes.
Metabolism: In humans, abacavir is not significantly metabolized by cytochrome P450 enzymes. The primary routes of elimination of abacavir are metabolism by alcohol dehydrogenase (to form the 5′-carboxylic acid) and glucuronyl transferase (to form the 5′-glucuronide). The metabolites do not have antiviral activity. In vitro experiments reveal that abacavir does not inhibit human CYP3A4, CYP2D6, or CYP2C9 activity at clinically relevant concentrations.
Elimination: Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of ^{14}C-abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose.
In single-dose studies, the observed elimination half-life ($t_{1/2}$) was 1.54 ± 0.63 hours. After intravenous administration, total clearance was 0.80 ± 0.24 L/hr/kg (mean ± SD).
Special Populations: ***Adults With Impaired Renal Function:*** The pharmacokinetic properties of ZIAGEN have not been determined in patients with impaired renal function. Renal excretion of unchanged abacavir is a minor route of elimination in humans.
Adults with Impaired Hepatic Function: The pharmacokinetics of abacavir have been studied in patients with mild hepatic impairment (Child-Pugh score 5 to 6). Results showed that there was a mean increase of 89% in the abacavir AUC, and an increase of 58% in the half-life of abacavir after a single dose of 600 mg of abacavir. The AUCs of the metabolites were not modified by mild liver disease; however, the rates of formation and elimination of the metabolites were decreased. A dose of 200 mg (provided by 10 mL of ZIAGEN Oral Solution) administered twice daily is recommended for patients with mild liver disease. The safety, efficacy, and pharmacokinetics of abacavir have not been studied in patients with moderate or severe hepatic impairment, therefore ZIAGEN is contraindicated in these patients.
Pediatric Patients: The pharmacokinetics of abacavir have been studied after either single or repeat doses of ZIAGEN in 68 pediatric patients. Following multiple-dose administration of ZIAGEN 8 mg/kg twice daily, steady-state $AUC_{(0-12\ hr)}$ and C_{max} were 9.8 ± 4.56 mcg•hr/mL and 3.71 ± 1.36 mcg/mL (mean ± SD), respectively (see PRECAUTIONS: Pediatric Use).
Geriatric Patients: The pharmacokinetics of ZIAGEN have not been studied in patients over 65 years of age.
Gender: The pharmacokinetics of ZIAGEN with respect to gender have not been determined.
Race: The pharmacokinetics of ZIAGEN with respect to race have not been determined.
Drug Interactions: In human liver microsomes, abacavir did not inhibit cytochrome P450 isoforms (2C9, 2D6, 3A4). Based on these data, it is unlikely that clinically significant drug interactions will occur between abacavir and drugs metabolized through these pathways.
Due to their common metabolic pathways via glucuronyl transferase with zidovudine, 15 HIV-infected patients were enrolled in a crossover study evaluating single doses of abacavir (600 mg), lamivudine (150 mg), and zidovudine (300 mg) alone or in combination. Analysis showed no clinically relevant changes in the pharmacokinetics of abacavir with the addition of lamivudine or zidovudine or the combination of lamivudine and zidovudine. Lamivudine exposure (AUC decreased 15%) and zidovudine exposure (AUC increased 10%) did not show clinically relevant changes with concurrent abacavir.
Due to their common metabolic pathways via alcohol dehydrogenase, the pharmacokinetic interaction between abacavir and ethanol was studied in 24 HIV-infected male patients. Each patient received the following treatments on separate occasions: a single 600-mg dose of abacavir, 0.7 g/kg ethanol (equivalent to 5 alcoholic drinks), and abacavir 600 mg plus 0.7 g/kg ethanol. Coadministration of ethanol and abacavir resulted in a 41% increase in abacavir AUC_∞ and a 26% increase in abacavir $t_{1/2}$. In males, abacavir had no effect on the pharmacokinetic properties of ethanol, so no clinically significant interaction is expected in men. This interaction has not been studied in females.
Methadone: In a study of 11 HIV-infected patients receiving methadone-maintenance therapy (40 mg and 90 mg daily), with 600 mg of ZIAGEN twice daily (twice the currently recommended dose), oral methadone clearance increased 22% (90% CI 6% to 42%). This alteration will not result in a methadone dose modification in the majority of patients; however, an increased methadone dose may be required in a small number of patients.

INDICATIONS AND USAGE

ZIAGEN Tablets and Oral Solution, in combination with other antiretroviral agents, are indicated for the treatment of HIV-1 infection.
Description of Clinical Studies: ***Therapy-Naive Adults:*** **CNA30024** was a multicenter, double-blind, controlled study in which 649 HIV-infected, therapy-naive adults were randomized and received either ZIAGEN (300 mg twice daily), lamivudine (150 mg twice daily), and efavirenz (600 mg once daily) or zidovudine (300 mg twice daily), lamivduine (150 mg twice daily), and efavirenz (600 mg once daily). The duration of double-blind treatment was at least 48 weeks. Study participants were: male (81%), Caucasian (51%), black (21%), and Hispanic (26%). The median age was 35 years; the median pretreatment CD4+ cell count was 264 cells/mm^3, and median plasma HIV-1 RNA was 4.79 log_{10} copies/mL. The outcomes of randomized treatment are provided in Table 1.
[See table 1 at top of next page]
After 48 weeks of therapy, the median CD4+ cell count increases from baseline were 209 cells/mm^3 in the group receiving ZIAGEN and 155 cells/mm^3 in the zidovudine group. Through Week 48, 8 subjects (2%) in the group receiving ZIAGEN (5 CDC classification C events and 3

Continued on next page

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due to a combination of their seriousness, frequency of reporting, or potential causal connection to ZOFRAN.

General: Flushing. Rare cases of hypersensitivity reactions, sometimes severe (e.g., anaphylaxis/anaphylactoid reactions, angioedema, bronchospasm; shortness of breath, hypotension, laryngeal edema, stridor) have also been reported. Laryngospasm, shock, and cardiopulmonary arrest have occurred during allergic reactions in patients receiving injectable ondansetron.

Hepatobiliary: Liver enzyme abnormalities

Lower Respiratory: Hiccups

Neurology: Oculogyric crisis, appearing alone, as well as with other dystonic reactions

Skin: Urticaria

DRUG ABUSE AND DEPENDENCE

Animal studies have shown that ondansetron is not discriminated as a benzodiazepine nor does it substitute for benzodiazepines in direct addiction studies.

OVERDOSAGE

There is no specific antidote for ondansetron overdose. Patients should be managed with appropriate supportive therapy. Individual intravenous doses as large as 150 mg and total daily intravenous doses as large as 252 mg have been inadvertently administered without significant adverse events. These doses are more than 10 times the recommended daily dose.

In addition to the adverse events listed above, the following events have been described in the setting of ondansetron overdose: "Sudden blindness" (amaurosis) of 2 to 3 minutes' duration plus severe constipation occurred in 1 patient that was administered 72 mg of ondansetron intravenously as a single dose. Hypotension (and faintness) occurred in a patient that took 48 mg of ZOFRAN Tablets. Following infusion of 32 mg over only a 4-minute period, a vasovagal episode with transient second-degree heart block was observed. In all instances, the events resolved completely.

DOSAGE AND ADMINISTRATION

Instructions for Use/Handling ZOFRAN ODT Orally Disintegrating Tablets: Do not attempt to push ZOFRAN ODT Tablets through the foil backing. With dry hands, PEEL BACK the foil backing of 1 blister and GENTLY remove the tablet. IMMEDIATELY place the ZOFRAN ODT Tablet on top of the tongue where it will dissolve in seconds, then swallow with saliva. Administration with liquid is not necessary.

Prevention of Nausea and Vomiting Associated With Highly Emetogenic Cancer Chemotherapy: The recommended adult oral dosage of ZOFRAN is a single 24-mg tablet administered 30 minutes before the start of single-day highly emetogenic chemotherapy, including cisplatin ≥50 mg/m^2. Multiday, single-dose administration of ZOFRAN 24-mg Tablets has not been studied.

Pediatric Use: There is no experience with the use of 24-mg ZOFRAN Tablets in pediatric patients.

Geriatric Use: The dosage recommendation is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Moderately Emetogenic Cancer Chemotherapy: The recommended adult oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given twice a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with a subsequent dose 8 hours after the first dose. One 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered twice a day (every 12 hours) for 1 to 2 days after completion of chemotherapy.

Pediatric Use: For pediatric patients 12 years of age and older, the dosage is the same as for adults. For pediatric patients 4 through 11 years of age, the dosage is one 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day. The first dose should be administered 30 minutes before the start of emetogenic chemotherapy, with subsequent doses 4 and 8 hours after the first dose. One 4-mg ZOFRAN Tablet or one 4-mg ZOFRAN ODT Tablet or 5 mL (1 teaspoonful equivalent to 4 mg of ondansetron) of ZOFRAN Oral Solution should be administered 3 times a day (every 8 hours) for 1 to 2 days after completion of chemotherapy.

Geriatric Use: The dosage is the same as for the general population.

Prevention of Nausea and Vomiting Associated With Radiotherapy, Either Total Body Irradiation, or Single High-Dose Fraction or Daily Fractions to the Abdomen:

The recommended oral dosage is one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution given 3 times a day.

For total body irradiation, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before each fraction of radiotherapy administered each day.

For single high-dose fraction radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy.

For daily fractionated radiotherapy to the abdomen, one 8-mg ZOFRAN Tablet or one 8-mg ZOFRAN ODT Tablet or 10 mL (2 teaspoonfuls equivalent to 8 mg of ondansetron) of ZOFRAN Oral Solution should be administered 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for each day radiotherapy is given.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of radiation-induced nausea and vomiting in pediatric patients.

Geriatric Use: The dosage recommendation is the same as for the general population.

Postoperative Nausea and Vomiting: The recommended dosage is 16 mg given as two 8-mg ZOFRAN Tablets or two 8-mg ZOFRAN ODT Tablets or 20 mL (4 teaspoonfuls equivalent to 16 mg of ondansetron) of ZOFRAN Oral Solution 1 hour before induction of anesthesia.

Pediatric Use: There is no experience with the use of ZOFRAN Tablets, ZOFRAN ODT Tablets, or ZOFRAN Oral Solution in the prevention of postoperative nausea and vomiting in pediatric patients.

Geriatric Use: The dosage is the same as for the general population.

Dosage Adjustment for Patients With Impaired Renal Function: The dosage recommendation is the same as for the general population. There is no experience beyond first-day administration of ondansetron.

Dosage Adjustment for Patients With Impaired Hepatic Function: In patients with severe hepatic impairment (Child-Pugh[2] score of 10 or greater), clearance is reduced and apparent volume of distribution is increased with a resultant increase in plasma half-life. In such patients, a total daily dose of 8 mg should not be exceeded.

HOW SUPPLIED

ZOFRAN Tablets, 4 mg (ondansetron HCl dihydrate equivalent to 4 mg of ondansetron), are white, oval, film-coated tablets engraved with "Zofran" on one side and "4" on the other in daily unit dose packs of 3 tablets (NDC 0173-0446-04), bottles of 30 tablets (NDC 0173-0446-00), and unit dose packs of 100 tablets (NDC 0173-0446-02).

ZOFRAN Tablets, 8 mg (ondansetron HCl dihydrate equivalent to 8 mg of ondansetron), are yellow, oval, film-coated tablets engraved with "Zofran" on one side and "8" on the other in daily unit dose packs of 3 tablets (NDC 0173-0447-04), bottles of 30 tablets (NDC 0173-0447-00), and unit dose packs of 100 tablets (NDC 0173-0447-02).

Bottles: Store between 2° and 30°C (36° and 86°F). Protect from light. Dispense in tight, light-resistant container as defined in the USP.

Unit Dose Packs: Store between 2° and 30°C (36° and 86°F). Protect from light. Store blisters in cartons.

ZOFRAN Tablets, 24 mg (ondansetron HCl dihydrate equivalent to 24 mg of ondansetron), are pink, oval, film-coated tablets engraved with "GX CF7" on one side and "24" on the other in daily unit dose packs of 1 tablet (NDC 0173-0680-00).

Store between 2° and 30°C (36° and 86°F).

ZOFRAN ODT Orally Disintegrating Tablets, 4 mg (as 4 mg ondansetron base) are white, round and plano-convex tablets debossed with a "Z4" on one side in unit dose packs of 30 tablets (NDC 0173-0569-00).

ZOFRAN ODT Orally Disintegrating Tablets, 8 mg (as 8 mg ondansetron base) are white, round and plano-convex tablets debossed with a "Z8" on one side in unit dose packs of 10 tablets (NDC 0173-0570-04) and 30 tablets (NDC 0173-0570-00).

Store between 2° and 30°C (36° and 86°F).

ZOFRAN Oral Solution, a clear, colorless to light yellow liquid with a characteristic strawberry odor, contains 5 mg of ondansetron HCl dihydrate equivalent to 4 mg of ondansetron per 5 mL in amber glass bottles of 50 mL with child-resistant closures (NDC 0173-0489-00).

Store upright between 15° and 30°C (59° and 86°F). Protect from light. Store bottles upright in cartons.

REFERENCES

1. Britto MR, Hussey EK, Mydlow P, et al. Effect of enzyme inducers on ondansetron (OND) metabolism in humans. *Clin Pharmacol Ther* 1997;61:228.
2. Pugh RNH, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Brit J Surg* 1973;60:646-649.
3. Villikka K, Kivisto KT, Neuvonen PJ. The effect of rifampin on the pharmacokinetics of oral and intravenous ondansetron. *Clin Pharmacol Ther* 1999;65:377-381.
4. De Witte JL, Schoenmaekers B, Sessler DI, et al. *Anesth Analg* 2001;92:1319-1321.
5. Arcioni R, della Rocca M, Romanò R, et al. *Anesth Analg* 2002;94:1553-1557.

ZOFRAN Tablets and Oral Solution:
GlaxoSmithKline, Research Triangle Park, NC 27709
ZOFRAN ODT Orally Disintegrating Tablets:
Manufactured for GlaxoSmithKline
Research Triangle Park, NC 27709
by Cardinal Health
Blagrove, Swindon, Wiltshire, UK SN5 8RU

May 2004/RL-2082

Shown in Product Identification Guide, page 318

ZOVIRAX® ℞
[zō-vī'rax]
(acyclovir)
Capsules

ZOVIRAX® ℞
(acyclovir)
Tablets

ZOVIRAX® ℞
(acyclovir)
Suspension

DESCRIPTION

ZOVIRAX is the brand name for acyclovir, a synthetic nucleoside analogue active against herpesviruses. ZOVIRAX Capsules, Tablets, and Suspension are formulations for oral administration. Each capsule of ZOVIRAX contains 200 mg of acyclovir and the inactive ingredients corn starch, lactose, magnesium stearate, and sodium lauryl sulfate. The capsule shell consists of gelatin, FD&C Blue No. 2, and titanium dioxide. May contain one or more parabens. Printed with edible black ink.

Each 800-mg tablet of ZOVIRAX contains 800 mg of acyclovir and the inactive ingredients FD&C Blue No. 2, magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each 400-mg tablet of ZOVIRAX contains 400 mg of acyclovir and the inactive ingredients magnesium stearate, microcrystalline cellulose, povidone, and sodium starch glycolate.

Each teaspoonful (5 mL) of ZOVIRAX Suspension contains 200 mg of acyclovir and the inactive ingredients methylparaben 0.1% and propylparaben 0.02% (added as preservatives), carboxymethylcellulose sodium, flavor, glycerin, microcrystalline cellulose, and sorbitol.

Acyclovir is a white, crystalline powder with the molecular formula $C_8H_{11}N_5O_3$ and a molecular weight of 225. The maximum solubility in water at 37°C is 2.5 mg/mL. The pka's of acyclovir are 2.27 and 9.25.

The chemical name of acyclovir is 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)methyl]-6*H*-purin-6-one.

VIROLOGY

Mechanism of Antiviral Action: Acyclovir is a synthetic purine nucleoside analogue with in vitro and in vivo inhibitory activity against herpes simplex virus types 1 (HSV-1), 2 (HSV-2), and varicella-zoster virus (VZV). The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (TK) encoded by HSV and VZV. This viral enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA. This is accomplished in 3 ways: 1) competitive inhibition of viral DNA polymerase, 2) incorporation into and termination of the growing viral DNA chain, and 3) inactivation of the viral DNA polymerase. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral TK.

Antiviral Activities: The quantitative relationship between the in vitro susceptibility of herpes viruses to antivirals and the clinical response to therapy has not been established in humans, and virus sensitivity testing has not been standardized. Sensitivity testing results, expressed as the concentration of drug required to inhibit by 50% the growth of virus in cell culture (IC_{50}), vary greatly depending upon a number of factors. Using plaque-reduction assays, the IC_{50} against herpes simplex virus isolates ranges from 0.02 to 13.5 mcg/mL for HSV-1 and from 0.01 to 9.9 mcg/mL for HSV-2. The IC_{50} for acyclovir against most laboratory strains and clinical isolates of VZV ranges from 0.12 to 10.8 mcg/mL. Acyclovir also demonstrates activity against the Oka vaccine strain of VZV with a mean IC_{50} of 1.35 mcg/mL.

Drug Resistance: Resistance of HSV and VZV to acyclovir can result from qualitative and quantitative changes in the viral TK and/or DNA polymerase. Clinical isolates of HSV and VZV with reduced susceptibility to acyclovir have been recovered from immunocompromised patients, especially with advanced HIV infection. While most of the acyclovir-resistant mutants isolated thus far from immunocompromised patients have been found to be TK-deficient mutants, other mutants involving the viral TK gene (TK partial and TK altered) and DNA polymerase have been isolated. TK-negative mutants may cause severe disease in infants and immunocompromised adults. The possibility of viral resistance to acyclovir should be considered in patients who show poor clinical response during therapy.

CLINICAL PHARMACOLOGY

Pharmacokinetics: The pharmacokinetics of acyclovir after oral administration have been evaluated in healthy volunteers and in immunocompromised patients with herpes simplex or varicella-zoster virus infection. Acyclovir pharmacokinetic parameters are summarized in Table 1.

Continued on next page

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Creatine

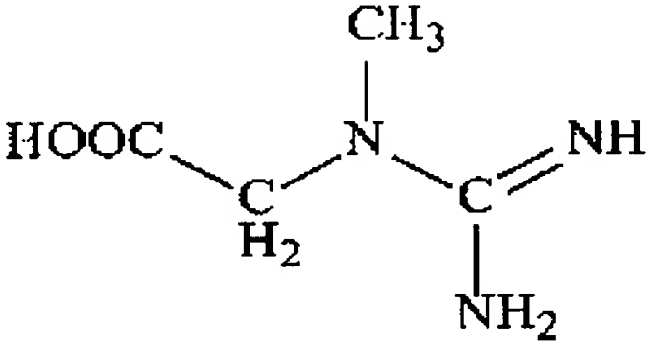
TRADE NAMES

Creatine is available generically from numerous manufacturers. Branded products include Muscle Power (Mason Vitamins), Creatine Fuel (Twinlab), Creatine Booster (Champion Nutrition), Creatigen (Bricker Labs), CreaVate (Prolab Nutrition), Perfect Creatine (Nature's Best), Xtra Advantage Creatine Serum (Muscle Marketing USA), Micronized Creatine (Met-Rx), Creavescent (GEN), Power Creatine (Champion Nutrition), Phosphagen (GNC), Crea-Tek (Iron Tek), Effervescent Creatine Elite (Muscle Link).

DESCRIPTION

Creatine is a non-protein amino acid found in animals and, in much lesser amounts, plants. Creatine is synthesized in the kidney, liver and pancreas from the amino acids L-arginine, glycine and L-methionine. Following its biosynthesis, creatine is transported to the skeletal muscle, heart, brain and other tissues. Most of the creatine is metabolized in these tissues to phosphocreatine (creatine phosphate). Phosphocreatine is a major energy storage form in the body.

Creatine is known chemically as N-(aminoiminomethyl)-N-methyl glycine and its structural formula is:



Creatine

Supplemental creatine is typically a synthetic substance. It is a solid and is water-soluble.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental creatine may have an energy-generating action during anaerobic exercise and may also have neuroprotective and cardioprotective actions.

MECHANISM OF ACTION

Since the action of supplemental creatine has yet to be clarified, the mechanism of action is a matter of speculation. Much is known, however, about the biochemistry of endogenous creatine. Creatine is mainly synthesized in the kidney, liver and pancreas. In its synthesis, the guanidino group of L-arginine is transferred to glycine to form guanidinoacetate and ornithine by a transamidinase reaction, a reaction that takes place in the pancreas, liver and kidney. Guanidinoacetate is methylated by S-adenosylmethione (SAMe) to form creatine. About 1 to 2 grams of creatine are biosynthesized daily and another 1 to 2 grams are obtained from diet.

In muscle and nerve, most of the creatine is phosphorylated to phosphocreatine (PCr) in a reaction that is

catalyzed by the enzyme creatine kinase (CK). There are three isoforms (isoenzymes) of CK. CK-MM is the skeletal muscle isoform; CK-BB, the brain isoform, and CK-MB, the isoform found in cardiac muscle. Most of the PCr in the body is in skeletal muscle.

Creatine, creatine kinase and phosphocreatine make up an intricate cellular energy buffering and transport system connecting sites of energy production in the mitochondria with sites of energy consumption. CK is a key enzyme involved in cellular energy homeostasis. It reversibly catalyzes the transfer of the high-energy phosphate bond in PCr to adenosine diphosphate (ADP) to form adenosine triphosphate (ATP), and it catalyzes the transfer of the high-energy phosphate bond in ATP to creatine to form PCr. During periods of intense exercise and skeletal muscle contraction, bioenergetic metabolism switches from one in which oxidative phosphorylation is the major pathway of ATP production to one in which so-called anaerobic glycolysis becomes dominant. Much less ATP would be generated during this period if it were not for phosphocreatine (PCr) being the only fuel available to regenerate ATP during this period. Thus the availability of PCr is the limiting factor of skeletal-muscle performance during high intensity and brief bursts (about 10 seconds) of activity. Supplemental creatine may increase PCr levels in skeletal muscle and hypothetically enhance ATP turnover during maximal exercise.

Creatine supplementation of transgenic amyotrophic lateral sclerosis (ALS) mice carrying the superoxide dismutase (SOD)1 mutation has reportedly produced improvement in motor performance and extension of survival, as well as protection against loss of both motor neurons and substantia nigra neurons. Mitochondrial dysfunction is among the earliest features found in these mice models of familial ALS. Creatine administration to these mice appears to stabilize mitochondrial CK and inhibits opening of the mitochondrial transition pores.

Creatine, as well as a creatine analogue called cyclocreatine, inhibit growth of a broad range of solid tumors in rat models of cancer; these tumors express high levels of CK. Although the mechanism of tumor inhibition is unknown, there is speculation about what it may be. Creatine feedback inhibits the transamidination step in its biosynthesis. This results in sparing L-arginine, the limiting precursor in creatine synthesis. More available L-arginine can lead to increased levels of nitric oxide (NO), which is a factor in macrophage activation. Another possibility is that glycolysis is inhibited in these tumors. Phosphocreatine inhibits enzymes in the glycolitic pathway, including glyceraldehyde-3-phosphate dehydrogenase, phosphofructokinase and pyruvate kinase.

PHARMACOKINETICS

Creatine is absorbed from the small intestine and enters the portal circulation and is transported to the liver. The ingested creatine, along with creatine made in the liver, is then transported into the systemic circulation and distributed to various tissues of the body, including muscle and nerves, by crossing the cell membrane via a specific creatine-transporter system against a 200:1 gradient. Chronic creatine supplementation in rats down-regulates creatine transporter protein expression. If this is also the case in humans, then chronic creatine supplementation would lead to lower amounts entering cells at any given time.

Within muscle and nerve cells, about 60 to 67% of the creatine entering the cells gets converted to phosphocreatine via the enzyme creatine kinase. About 2% of creatine is converted to creatinine, and both creatine and creatinine are excreted by the kidneys.

INDICATIONS AND USAGE

There is some evidence that supplemental creatine may enhance performance in a limited number of high-intensity, short-term physical activities, but the data are mixed, and no ergogenic effect has been convincingly demonstrated outside of laboratory settings. Adequate safety data are still lacking. There is some very preliminary data that creatine may be helpful in treating muscular dystrophy and amyotrophic lateral scleroses and may improve skeletal muscle function in some with congestive heart failure and gyrate atrophy of the retina. Creatine has inhibited the growth of some solid tumors in rats, but no human cancer data exist.

RESEARCH SUMMARY

Limited muscle function benefit has been noted in some early studies of creatine. All of these studies have been of short duration (mostly lasting one or two weeks and, in no case, more than eight weeks). Many other studies have found no benefit.

A recent review article summarized the results of 71 trials published between 1993 and 1997. Of those that studied effects of supplemental creatine (usually 20 grams daily for 4 to 21 days) on short term, high-intensity performance, 23 reported positive effects and 20 reported no effect. Studies examining the effects of creatine on oxidative energy systems, muscle isokinetic torque and isometric force produced similarly mixed results. Among the few field tests that have been conducted (all related to swim sprints) none detected any effect on athletic performance. Only among studies of cycle ergometer performance was there any superiority of creatine over placebo (11 trials reported improvement, while six others reported no improvement).

Since this review was published there have been a few more positive than negative reports, but, again, the positive effects are almost entirely seen in laboratory settings and are confined to short-term, high-intensity performance.

One author recently reviewed the creatine data and has concluded that supplemental creatine achieves an

ergogenic effect, at least in the laboratory, in repeated stationary cycling sprints. But he found no convincing evidence that it does so in single sprints. He also discerned a possible ergogenic effect in weightlifting, but none in running or swimming sprints of any kind. He and others have speculated that the weight gain that typically accompanies creatine supplementation offsets any ergogenic effect that might otherwise benefit runners and swimmers.

Some have claimed that this weight gain, typically 0.5 to 1.6 kilograms occurring in the first few days to first two weeks of creatine supplementation, is evidence of increased muscle mass. Most researchers, however, believe that this weight gain is accounted for by creatine-induced water retention. The longer-term studies needed to confirm or refute claims that chronic creatine supplementation can result in greater muscle mass have not been conducted.

Another caveat offered by several researchers is that almost all of the positive creatine effects so far noted have been achieved in laboratory tests of elite athletes and were observed only in the sort of maximal intermittent exercise that non-athletes can rarely achieve. No benefit for any aerobic activity has been demonstrated.

In addition, safety data are lacking and are urgently needed, especially for long-term use of creatine and for use among the pediatric population (including adolescents) and among those in poor health. There are some reports that long-term use of creatine may be nephrotoxic. This needs further investigation before long-term creatine supplementation can be recommended under any circumstance.

Possible additional uses for creatine have been suggested by preliminary work. There is some evidence of creatine synthesis in the retina, and supplementation with 1.5 grams of creatine daily for a year has been reported to bring improvement in genetic gyrate atrophy--not in the blindness that results from this condition but in the skeletal muscle abnormalities that also characterize it. Giving 5 grams of creatine four times a day for a period of five days has similarly been reported to improve skeletal muscle function in some with congestive heart failure. The effect was small.

In a mouse model of amyotrophic lateral sclerosis (ALS), supplemental creatine significantly prolonged survival. Improvement was seen on motor-performance tests, and there was histologic evidence of neuron protection associated with creatine supplementation. Because creatine protected neurons in the substantia nigra, there is speculation that the supplement could also have positive effects in Parkinson's disease.

These researchers have suggested that creatine may exert the favorable results seen in the mouse model through an intracellular energy-buffering effect that may help prevent the sort of mitochondrial dysfunction that they postulate plays a role in neuronal cell death. More research is needed.

Another recent, preliminary report asserts a positive role for supplemental creatine in the treatment of muscular dystrophy and some other neuromuscular disorders. This study tested 10 grams of creatine daily for five days, followed by 5 grams daily for an additional 5 to7 days, against placebo. Increases were noted in handgrip, ankle and knee strength among those taking creatine. Again, more research is needed.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Creatine is contraindicated in those with renal failure and renal disorders such as nephrotic syndrome.

PRECAUTIONS

Creatine supplements should be avoided by children, adolescents, pregnant women, nursing mothers and anyone at risk for renal disorders such as diabetics. Those taking creatine should have serum creatinine levels monitored.

ADVERSE REACTIONS

The deaths of three American college wrestlers had been linked to the use of creatine supplements. However, results of post mortem tests led to the conclusion that the deaths were caused by severe dehydration and renal failure, and were not due to creatine. Apparently, the wrestlers were trying to lose enough weight through perspiration to allow them to compete in lower-weight classes. Typical adverse effects are gastrointestinal and include nausea, diarrhea and indigestion. Also common are muscle cramping and strains. Weight gain may occur from water retention. During a five day loading period, weight gains of 1.1 to 3.5 pounds have been reported. There are reports of elevated serum creatinine, a metabolite of creatine and a marker of kidney function, in some who take creatine and have normal renal function. This is reversible upon discontinuation of creatine.

Anecdotal reports of adverse events to FDA have included rash, dyspnea, vomiting, diarrhea, nervousness, anxiety, migraine, fatigue, polymyositis, myopathy, seizures and atrial fibrillation.

INTERACTIONS

There are as yet no known drug, nutritional supplement or herb interactions. Caffeine (in coffee, tea and caffeinated beverages) appears to interfere with any beneficial effects of creatine supplementation.

DOSAGE AND ADMINISTRATION

The typical form of creatine available is a creatine monohydrate powder.

The dosing for those who use creatine to attempt to improve performance in brief, high-intensity activities, is a loading dose of 20 grams or 0.3 grams per kilogram in divided doses four times a day for two to five days, followed by a maintenance dose of no more than 2 grams daily or 0.03 grams per kilogram. Those who use creatine supplements should take them with adequate water, six to eight glasses per day.

HOW SUPPLIED

Capsules — 700 mg, 725 mg, 750 mg, 1200 mg

Effervescent Tablets — 5 gm

Effervescent Powder — 27 gm/packet

Powder — 5 gm/tsp

Wafers — 1000 mg

LITERATURE

Feldman EB. Creatine: a dietary supplement and ergogenic aid. *Nutr Rev*.1999; 57:45-50.

Greenhoff PL. Creatine and its application as an ergogenic aid. *Int J Sport Nutr.* 1995; 5:S100-S110.

Juhn MS. Oral creatine supplementation. *Phys Sports Med*. 1999; 27;47-45..

Klivenyi P, Ferrante RJ, Matthews RT, et al. Neuroprotective effects of creatine in a transgenic animal model of amyotrophic lateral sclerosis, *Nat Med*. 1999; 5:47-350.

Koshy KM, Griswald E, Sneeberger EE. Interstitial nephritis in a patient taking creatine. *N Engl J Med*. 1999; 340:814-815.

Miller EE, Evans AE, Cohn M. Inhibitions of rate of tumor growth by creatine and cyclocreatine. *Proc Natl Accd Sci USA*. 1993; 90:3304-3308.

Poortman JR, Augier H, Renaut V, et al. Effect of short-term creatine supplementation on renal responses in men. *Eur J Appl Physiol*. 1997; 76:566-567.

Sipila I, Rapola J, Simell O, et al. Supplemental creatine as a treatment for gyrate atrophy of the choroid and retina. *N Engl J Med*. 1981; 304:867-870.

Tarnopolsky M, Martin J. Creatine monohydrate increases strength in patients with neuromuscular disease. *Neurology*. 1999; 52:854-857.

Toler SM. Creatine is an ergogenic for anaerobic exercise. *Nutr Rev*. 1997; 55:21-23.

Vandenberghe K, Gillis N. Van Leemputte M, et al. Caffeine counteracts the ergogenic action of muscle creatine loading. *J Appl Physiol*. 1996; 80:452-457.

Williams MH, Branch JD. Creatine supplementation and exercise performance: an update. *J Am Coll Nutr*. 1998; 17:216-234.

Thiamin (Vitamin B_1)

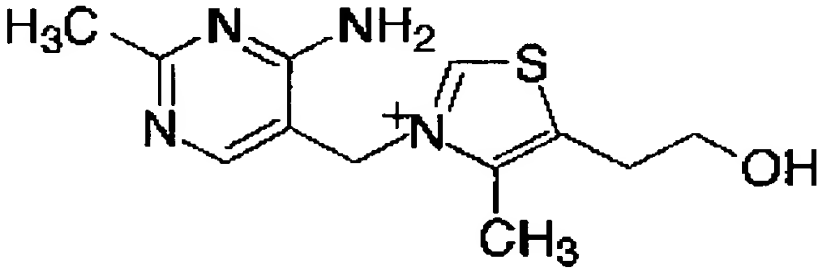
TRADE NAMES

Thiamilate (Tyson Neutraceuticals), Bethamine (Ampharco Inc.).

DESCRIPTION

In 1911, the chemist Casimir Funk isolated a substance from rice bran extracts which he thought was the anti-beriberi factor. Because the substance was an amine and because he thought the substance had a vital dietary function, he named it vitamine. As it turned out, Funk's vitamine was not the anti-beriberi factor which was subsequently isolated and called thiamin or vitamin B_1. Nevertheless, Funk did coin the term vitamin and the concept that vitamins are essential dietary factors.

Thiamin is a water-soluble vitamin. Structurally it consists of a substituted pyrimidine ring joined by a methylene bridge to a substituted thiazole ring. The free vitamin is a base. The thiazolium salts of thiamin, thiamin hydrochloride and thiamin mononitrate, are the forms of thiamin which are typically used in nutritional supplements and for food fortification. In addition to being known as vitamin B_1, thiamin is known as thiamine, aneurin and 3-[(4-amino-2-methyl-5-pyrimidinyl) methyl]-5-(2-hydroxyethyl)-4-methyl-thiazonium. The structural formula of thiamin follows:



Thiamin

The classic deficiency state of thiamin is beriberi. An analogous disorder in fowl is called polyneuritis. The term beriberi is derived from the Sinhalese word meaning extreme weakness. Beriberi was very common during the early part of the last century in those whose diets consisted principally of highly polished rice. Interestingly, those who ate parboiled rice—partially boiled rice—did not develop beriberi. Milling removes the husk, which contains most of the thiamin, while parboiling the rice before husking disperses thiamin throughout the grain. Beriberi still occurs in those whose diet mainly consists of polished rice. Thiamin deficiency is also associated with alcoholism and occurs in some cases of malnutrition, those receiving total parenteral nutrition without thiamin, malabsorption syndromes, increased carbohydrate intake, major catabolic and physiologic stress states, acute infection, folate deficiency, thyrotoxicosis and those on long-term loop diuretics (furosemide, ethacrynic acid, bumetanide). Subclinical thiamin deficiency may not be uncommon.

There are three types of beriberi: dry beriberi, wet beriberi and cerebral beriberi or Wernicke-Korsakoff syndrome. Dry or neurologic beriberi occurs when thiamin deficiency affects the peripheral nervous system resulting in peripheral neuropathy. The peripheral neuropathy is characterized by a bilateral, symmetric impairment of sensory, motor and reflex functions involving predominantly the lower extremities. Symptoms and signs of dry beriberi, include paresthesias of the toes, burning of the feet, calf muscle tenderness and cramps, difficulty in rising from a squatting position, a decrease in the vibratory sensation in the toes, loss of ankle and knee jerks and footdrop and toedrop. Wet or cardiovascular beriberi involves the heart and circulatory system. Cardiovascular manifestations of thiamin deficiency are characterized by peripheral vasodilatation with increased cardiac output, sodium and water retention and myocardial failure. The most extreme form of wet beriberi is shoshin beriberi. Shoshin is Japanese for damage to the heart and is characterized by global heart failure with lactic acidosis in the context of blood tests showing thiamin deficiency. Shoshin beriberi, if not promptly treated, is rapidly fatal. Alcoholics who present with unexplained lactic acidosis, a hyperdynamic state and high output failure, or cardiogenic shock without evidence of a myocardial infarction, are unlikely to have anything but Shoshin beriberi.

Alcoholism is the major cause of thiamin deficiency in Wernicke-Korsakoff syndrome or cerebral beriberi. Wernicke-Korsakoff syndrome is characterized by abnormal ocular motor signs, ataxia and derangement of mental functions. The ocular motor signs include paresis of abduction which is accompanied by horizontal diplopia, strabismus and nystagmus. Derangement of mental functions include a global-confusional apathetic state and amnesia. Wernicke-Korsakoff syndome represents the full-blown clinical state of cerebral beriberi. Wernicke's disease itself is characterized by abnormal ocular motor signs and ataxia without an evident amnesic state. Korsakoff's psychosis itself is characterized by the mental derangements mentioned above.

Thiamin occurs in cells principally in its active coenzyme form called thiamin pyrophosphate (TPP, cocarboxylase). Thiamin, in the form of thiamin pyrophosphate, plays an essential role as a cofactor in key reactions in carbohydrate metabolism. It is also involved in the metabolism of branched-chain amino acids and may have non-coenzyme (non-cofactor) roles in excitable cells. TPP is a coenzyme in the oxidative decarboxylation of pyruvate to acetyl-coenzyme A (acetyl-CoA), of alpha-ketoglutarate to succinyl-CoA, and of the oxidative decarboxylation of the branched-chain alpha-keto acids, which are metabolites of the branched-chain amino acids L-leucine, L-isoleucine and L-valine. TPP is also a cofactor in the reversible transketolase reactions in the phosphogluconate pathway, also know as the pentose phosphate pathway and the hexose monophosphate shunt. The two transketolase reactions are the reversible conversions of D-xylulose 5-phosphate and D-ribose 5-phosphate to D-sedoheptulose 7-phosphate and D-glyceraldehyde 3-phosphate, and D-xylulose-5-phosphate and D-erythrose-4-phosphate to D-fructose 6-phosphate and D-glyceraldehyde 3-phosphate. The first of these two reactions represents the pathway for the non-oxidative production of ribose.

The total metabolic pool of thiamin in the body is approximately 30 milligrams. The predominant form of thiamin in the body is thiamin pyrophosphate (TPP, also known as thiamin diphosphate or TDP and cocarboxylase). Approximately 80% of thiamin in blood is present in erythrocytes as TPP. About 50% of total body thiamin is present in skeletal muscles. Thiamin is also found in heart, liver kidneys and brain. Other forms of thiamin present in the body include, thiamin triphosphate (TTP, about 10%), thiamin monophosphate (TMP) and free thiamin. TMP and free thiamin comprise about 10% of total body thiamin. The most reliable method of evaluating thiamin status is the measurement of erythrocyte transketolase activity and the percentage enhancement of the transketolase activity resulting from added thiamin pyrophosphate.

All plant and animal foods contain thiamin. Good dietary sources of the vitamin, include whole-grain products, brown rice, meat products, vegetables, fruits, legumes and seafood.

ACTIONS AND PHARMACOLOGY

ACTIONS

Thiamin may have antioxidant, erythropoietic, cognition-and mood-modulatory, antiatherosclerotic and detoxification activities. It has putative ergogenic activity.

MECHANISM OF ACTION

Thiamin has been found to protect against lead-induced lipid peroxidation in rat liver and kidney. Thiamin deficiency results in selective neuronal death in animal models. The neuronal death is associated with increased free radical production, suggesting that oxidative stress may play an important early role in brain damage associated with thiamin deficiency. The mechanism of the possible antioxidant activity of thiamin is unknown.

Even though anemia is not one of the consequences of thiamin deficiency, there is a type of anemia, called thiamin-responsive megaloblastic anemia, that responds well to large doses of thiamin. It is thought that those with thiamin-responsive megaloblastic anemia may actually be thiamin-deficient secondary to reduced thiamin transport and absorption, and to impaired intracellular thiamin pyrophosphorylation.

Thiamin deficiency is associated with cognitive and emotional changes. For example, Korsakoff's psychosis is characterized by the inability to form new memories, the poorly organized retrieval of remote memories, apathy and emotional blandness. The treatment of Korsakoff's patients with thiamin often results in significant improvement in these symptoms. Marginal thiamin deficiency may also result in cognitive and emotional changes. There are a few studies suggesting that high-dose thiamin supplementation may have a positive effect on mood and cognition in those with marginal deficiency, and even adequate status, of the vitamin. In one study with female subjects, improved thiamin status was associated with improved mood, and a decline in thiamin status was associated with poorer mood. In another study, again with female subjects, those taking 50 milligrams of thiamin daily for 20 months were found to have improvement in thiamin status associated with reports of being more clearheaded, composed and energetic. Reaction times were also faster. The study was placebo-controlled and performed in subjects whose thiamin status was adequate. The mechanism of the neurophysiological actions of thiamin are not well understood. Thiamin may play a role in neurophysiology independent of its coenzyme function. Thiamin is located in nerve cell membranes and phosphorylated forms of thiamin are associated with sodium channel proteins. It is thought that phosphorylated forms of thiamin may play roles in the control of sodium conductance at axonal membranes and in other neurological processes.

Migration and proliferation of arterial smooth muscle cells are thought to play an important role in the development of atherosclerosis. Glucose and insulin have been found to have an additive effect on the proliferation of infragenicular arterial smooth muscle cells *in vitro*. Thiamin has been found to inhibit human infragenicular arterial muscle cell proliferation induced by high glucose and insulin, in cell culture. Thiamin plays a key role in intracellular glucose metabolism and it is thought that thiamin inhibits the effect of glucose and

insulin on arterial smooth muscle cell proliferation. However, the mechanism of this *in vitro* effect is not well understood. Inhibition of endothelial cell proliferation may also promote atherosclerosis. Endothelial cells in culture have been found to have a decreased proliferative rate and delayed migration in response to hyperglycemic conditions. Thiamin has been shown to inhibit this effect of glucose on endothelial cells. It is thought that the mechanism of action of thiamin on endothelial cells is related to a reduction in intracellular protein glycation by redirecting the glycolytic flux. Atherosclerosis and peripheral artery disease are significant problems in those with type 2 diabetes mellitus. Further study of the possible anti-atherosclerotic activity of thiamin, particularly in those with type 2 diabetes, is warranted.

Some animal studies have found that high doses of thiamin block some of the toxic symptoms from orally administered lead. Thiamin may protect against lead toxicity by inhibiting lead-induced lipid peroxidation.

There are few studies investigating the effect of large doses of thiamin as an aid to exercise performance. In one such study, carbohydrate-loaded mice administered very high doses of thiamin demonstrated an improvement in swim time to exhaustion. In another study, experienced cyclists administered 900 milligram daily of thiamin for three days were found to have lower exercise heart rates, blood glucose and blood lactate concentrations. In still another study, thiamin supplementation at 100 milligram/day was found to decrease exercise-induced fatigue in male athletes. A recent study, however, using a thiamin derivative, thiamin tetrahydrofurfuryl disulfide, which is better absorbed than thiamin, showed no effect on high-intensity exercise performance. There is insufficient evidence to suggest that thiamin may have exercise performance-enhancing activity. The possible mechanism of this putative effect is unknown.

PHARMACOKINETICS

Thiamin is absorbed from the lumen of the small intestine—mainly the jejunum—by active transport and passive diffusion mechanisms. At lower amounts, absorption from the small intestine is by an active, carrier-mediated process that is energy-dependent as well as sodium-dependent. Passive diffusion occurs with higher amounts of thiamin. Absorption of thiamin appears to be limited by a saturable rate-limiting transport mechanism. Only a small percentage of a high dose of thiamin is absorbed. Certain lipid-soluble thiamin derivatives known as allithiamins, do not appear to be subject to the rate-limiting transport mechanism. Thiamin is transported by the portal circulation to the liver and by the systemic circulation to various tissues in the body. Thiamin is metabolized to thiamin monophosphate (TP, TMP), thiamin pyrophosphate (TPP, cocarboxylase, thiamin diphosphate, TDP) and thiamin triphosphate (TTP). Thiamin is phosphorylated directly to thiamin pyrophosphate by thiamin diphosphokinase and thiamin pyrophosphate is dephosphorylated to thiamin monophosphate via thiamin diphosphatase. Approximately 80% of thiamin in blood is present in erythrocytes as TPP. The transport of thiamin into erythrocytes appears to occur by facilitated diffusion; it enters other cells by an active process. Total thiamin content in the adult body is about 30 milligrams. Thiamin and its metabolites are mainly excreted by the kidneys.

INDICATIONS AND USAGE

Frank and marginal thiamin deficiency may not be uncommon and may be a particular problem among alcoholics, the elderly and the chronically ill. Thiamin supplementation may be useful in these subgroups, among others. There is evidence that supplemental thiamin can help protect against some of the metabolic imbalances caused by heavy alcohol consumption. It may help protect against Wernicke's encephalopathy and some other forms of brain damage seen in some alcoholics, some with HIV-disease, some with anorexia nervosa and others. It may be helpful in alcohol withdrawal. It is needed in those who receive total parenteral nutrition, particularly to prevent lactic acidosis due to thiamin deficiency. It may increase glucose tolerance and may help prevent atherosclerosis, particularly in diabetics. It has been used in congestive heart failure with benefit under certain circumstances and may be helpful in some other forms of heart disease. There is preliminary evidence that it can improve mood and cognition in some. Data are in short supply and results mixed with respect to claims that thiamin can enhance exercise performance and increase energy. Thiamin's use in cancer might be ill-advised, as there is evidence that it may promote tumor-cell proliferation.

RESEARCH SUMMARY

Alcoholics are at particularly high risk of thiamin deficiency. Alcohol interferes with the absorption of thiamin and its storage in tissue. It also inhibits conversion of thiamin to its active form. In addition, alcoholics generally have unbalanced diets low in thiamin. Some alcoholics suffer from frank beriberi, which, among other things, can lead to congestive heart failure. More frequently, alcoholics suffer from such beriberi symptoms as mental confusion, visual disturbances and staggering gait. Beriberi can be prevented and, in some cases, successfully treated with high doses of thiamin (up to 100 milligrams daily).

Thiamin can also help prevent some cases of Wernicke's encephalopathy, a potentially fatal disorder that occurs in some who consume very large amounts of alcohol. Symptoms include double vision, mental confusion, muscle weakness and disturbed gait. Untreated, this disorder can result in permanent brain damage and memory impairment. In extreme cases it leads to coma and death. It is often reversible with prompt thiamin treatment. Some use thiamin as part of alcohol-withdrawal therapy.

Others at higher than average risk of Wernicke's encephalopathy include those suffering from anorexia nervosa, typically young women. Older people are also at higher risk. So are people with HIV disease. Thiamin deficiency was found in 23% of HIV patients in one study, and brain lesions characteristic of those found in sufferers of Wernicke's encephalopathy have been seen in some with HIV-disease. Some researchers have recommended dietary thiamin supplementation in all newly diagnosed cases of HIV-disease.

It is now recognized that thiamin deficiency may occur with total parenteral nutrition (TPN). Several cases of lactic acidosis have been reported in TPN patients not receiving thiamin. Administration of thiamin has resolved the acidosis with attendant clinical improvement. Researchers stress that thiamin deficiency should always be included in the differential diagnosis of lactic acidosis. A recent shortage of multivitamin preparations for TPN is said to have resulted in a number of cases of lactic acidosis due to thiamin deficiency. A previous shortage led to several TPN-related deaths.

Thiamin deficiency is associated with abnormal glucose tolerance, and there is some evidence that supplemental thiamin may, in some cases, help correct the abnormality. In a recent *in vitro* study, thiamin inhibited accelerated proliferation of arterial smooth muscle cells. This proliferation contributes to atherosclerosis and preferentially affects the infragenicular vasculature in patients with diabetes mellitus. High insulin and glucose levels demonstrate additive effects in this process *in vitro*. This research gives some preliminary indication that thiamin may help prevent or delay atherosclerotic complications in some diabetics.

Thiamin supplementation has improved left ventricular function in patients with congestive heart failure being administered long-term furosemide therapy and, as noted above, supplemental thiamin can help prevent and treat heart disease related to beriberi. In addition, intravenous injection of thiamin proved helpful in an animal model of myocardial infarction, increasing strength of contractions and decreasing oxygen demand. Russian researchers have reported similar results in humans. Thiamin pyrophosphate (cocarboxylase) was used in these heart attack experiments. Research is needed to see whether thiamin itself might be beneficial.

Thiamin was found to have positive effects on mood and cognitive functioning in a recent study of 120 young females. In a previous study, females receiving a multi-vitamin supplement for three months were said to have improved mood compared with controls who received placebo. Using biochemical indices, an association was made between thiamin status and improved mood. These same measures did not support an association between any of eight other vitamins and elevated mood.

In this recent study, focus was on thiamin alone among the vitamins. All but one of the 120 women had normal thiamin levels at baseline. They were randomized to receive 50 milligrams of thiamin daily or placebo. After two months, the thiamin group significantly improved (more than doubled) their scores on the clear-headedness and mood subsets of the bipolar profile of mood states psychological test. There was no change in these measures in the placebo group. The thiamin group also showed nonsignificant improvement in feelings of confidence, composure and elation. The researchers considered their findings remarkable given that they were obtained in a group which, as measured by transketolase activation, had normal thiamin nutrition. More research is warranted.

Thiamin and a thiamin derivative have not shown any effect on exercise performance in two studies. High-dose thiamin (100 milligrams daily) was found to be helpful in preventing or accelerating recovery from exercise-induced fatigue in a third study. This trial tested thiamin in 16 male volunteer athletes using bicycle ergometer exercises. Followup is needed.

Finally, a group of researchers have recently called thiamin supplementation "a double-edged sword" in cancer patients. Like other seriously ill patients, cancer sufferers may benefit from improved thiamin status in terms of general nutrition, but, as these researchers observed, there is some evidence that thiamin may also, in effect, nourish some cancers. There is some indication that high-dose thiamin supplementation may promote tumor cell proliferation. More research is needed to help clarify this issue.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Thiamin contraindicated in those hypersensitive to any component of a thiamin-containing product.

PRECAUTIONS

The use of thiamin for the treatment of a thiamin-deficiency state, lactic acidosis secondary to thiamin-deficiency, Wernicke-Korsakoff syndrome, Wernicke's encephalopathy, Korsakoff's psychosis or any medical condition must only be undertaken under medical supervision.

A typical dose of thiamin used in pre- and postnatal multivitamin/multimineral supplements is three milligrams daily. Pregnant women and nursing mothers should avoid intakes of thiamin greater than this amount unless higher doses are prescribed by their physicians.

Those who are treated with parenteral thiamin for thiamin deficiency, should be given the thiamin prior to receiving parenteral glucose. Administration of intravenous glucose prior to receiving thiamin could result in severe lactic acidosis.

ADVERSE REACTIONS

Oral thiamin is well tolerated even at doses up to 200 milligrams daily or higher. There have been occasional reports of serious and even fatal responses to parenteral thiamin. These have probably been anaphylactic

reactions. There are also reports of less serious allergic reactions to parenteral thiamin.

There is some animal evidence that high doses of parenteral thiamin may promote tumor growth.

INTERACTIONS

DRUGS

Loop diuretics (furosemide, ethacrynic acid, bumetanide): Chronic use of loop diuretics may result in thiamin deficiency. Chronic use of furosemide for the treatment of congestive heart failure has been reported to result in thiamin deficiency. Thiamin repletion in such patients can improve left ventricular function.

FOODS

Substances in food that inactivate thiamin are called anti-thiamin factors.

Sulfites: Concomitant intake of thiamin and foods and beverages containing sulfites may inactivate thiamin.

Tea, coffee and decaffeinated coffee: Concomitant intake of these beverages and thiamin may inactivate thiamin. Tannic acid is most likely the substance in tea that inactivates thiamin by forming a tannin-thiamin adduct.

OVERDOSAGE

Overdosage of thiamin has not been reported in the literature.

DOSAGE AND ADMINISTRATION

Thiamin is available in nutritional supplements in the form of thiamin hydrochloride and thiamin nitrate. These are also the forms used for food fortification. Thiamin pyrophosphate or cocarboxylase may also be available in some products. Supplemental doses of thiamin are variable and range from the U.S. RDA amount of 1.5 milligrams/day to 10 milligrams/day or higher. There is a rapid decline in absorption that occurs at oral doses above five milligrams. Thiamin is typically found in the form of multivitamin, multivitamin/multimineral or B-complex preparations. Single ingredient thiamin supplements are also available. Pre- and postnatal supplements typically deliver a thiamin dose of 3 milligrams daily.

Lipid-soluble thiamin derivatives called allithiamins are also available. These forms are better absorbed at higher intakes than is thiamin.

The Food and Nutrition Board of the Institute of Medicine of the National Academy of Sciences recommends the following dietary reference intakes (DRIs) for thiamin:

Infants	Adequate Intakes (AI)
0-6 months	0.2 mg/day 0.03 mg/kg
7-12 months	0.3 mg/day 0.03 mg/kg
	Recommended Dietary
Children	Allowances (RDA)
1-3 years	0.5 mg/day
4-8 years	0.6 mg/day
Boys	
9-13 years	0.9 mg/day

14-18 years	1.2 mg/day
Girls	
9-13 years	0.9 mg/day
14-18 years	1.0 mg/day
Men	
19 years and older	1.2 mg/day
Women	
19 years and older	1.1 mg/day
Pregnancy	
14-50 years	1.4 mg/day
Lactation	
14-50 years	1.4 mg/day

The U.S. RDA for thiamin, which is used for determining percentage of daily values on nutritional supplement and food labels, is 1.5 milligrams.

HOW SUPPLIED

Vitamin B_1 is available in the following forms and strengths for Rx use:

Injection — 100 mg/mL

Vitamin B_1 is available in the following forms and strengths for OTC use:

Capsules — 100 mg, 500 mg

Enteric Coated Tablets — 20 mg

Tablets — 25 mg, 50 mg, 100 mg, 250 mg, 500 mg

LITERATURE

Avena R, Arora S, Carmody BJ, et al. Thiamin (vitamin B_1) protects against glucose- and insulin-mediated proliferation of human infragenicular arterial smooth muscle cells. *Ann Vasc Surg.* 2000; 14:37-43.

Bakker SJL, Hoogeveen EK, Nijpels G, et al. The association of dietary fibres with glucose tolerance is partly explained by concomitant intake of thiamin: The Hoorn Study. *Diabetologia*. 1998; 41:1168-1175.

Benton D, Griffiths R, Haller J. Thiamin supplementation mood and cognitive functioning. *Psychopharmacol.* 1997; 129:66-71.

Bettendorff L. A non-cofactor role of thiamin derivatives in excitable cells? *Arch Physiol Biochem*. 1996; 104:745-751.

Blanc P, Boussuges A. [Cardiac beriberi]. [Article in French]. *Arch Mal Coeur Vaiss*. 2000; 93:371-379.

Boros LG. Population thiamine status and varying cancer rates between western, Asian and African countries.

Anticancer Res. 2000; 20(3B):2245-2248.

Boros LG, Brandes JL, Lee WN, et al. Thiamine supplementation to cancer patients: a double edge sword. *Anticancer Res.* 1998; 18(1B):595-602.

Boros LG, Comin B, Boren J, et al. Over-expression of transketolase: a mechanism by which thiamine supplementation promotes cancer growth. *Am Assoc Cancer Res.* 2000; 41:66(Ab #4234).

Butterworth RF, Gaudreau C, Vincelette J, et al. Thiamin deficiency and Wernicke's encephalopathy in AIDS. *Metab Brain Dis.* 1991; 6:207-212.

Dietary Reference intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1998.

Frank T, Bitsch R, Maiwald J, Stein G. High thiamine diphosphate concentrations in erythrocytes can be achieved in dialysis patients by oral administration of benfotiamine. *Eur J Clin Pharmacol.* 2000; 56:251-257.

Hàrdig L, Daae C, Dellborg M, et al. Reduced thiamine phosphate, but not thiamine diphosphate, in erythrocytes in elderly patients with congestive heart failure treated with furosemide. *J Int Med.* 2000; 247:597-600.

La Selva M, Beltramo E, Pagnozzi F, et al. Thiamine corrects delayed replication and decreases production of lactate and advanced glycation end-products in bovine retinal and human umbilical vein endothelial cells cultured under high glucose conditions. *Diabetologia.* 1996; 39:1263-1268.

Muri RM, Von Overbeck J, Furrer J, Ballmer PE. Thiamin deficiency in HIV-positive patients: evaluations by erythrocyte transketolase activity and thiamin pyrophosphate effect. *Clin Nutr.* 1999; 18:375-378.

Pekovich SR, Martin PR, Singleton CK. Thiamine deficiency decreases steady-state transketolase and pyruvate dehydrogenase but not alpha-ketoglutarate dehydrogenase mRNA levels in three human cell types. *J Nutr.* 1998; 128:683-687.

Romanski SA, McMahon MM. Metabolic acidosis and thiamine deficiency. *Mayo Clin Proc.* 1999; 74:259-263.

Sato Y, Nakagawa M, Higuchi I, et al. Mitochondrial myopathy and familial thiamine deficiency. *Muscle Nerve.* 2000; 23:1069-1075.

Senapati SK, Dey S, Dwivedi SK, et al. Effect of thiamine hydrochloride on lead induced lipid peroxidation in rat liver and kidney. *Vet Hum Toxicol.* 2000; 42:236-237.

Shimon I, Almog S, Vered Z, et al. Improved left ventricular function after thiamine supplementation in patients with congestive heart failure receiving long-term furosemide therapy. *Am J Med.* 1995; 98:485-490.

Suter PM, Haller J, Hany A. Diuretic use: a risk for subclinical thiamine deficiency in elderly patients. *J Nutr Health Aging.* 2000; 4:69-71.

Suzuki M, Itokawa Y. Effects of thiamine supplementation on exercise-induced fatigue. *Metab Brain Dis.* 1996; 11:95-106.

Tanphaichitr V. Thiamin. In: Shils ME, Olson JA, Shike M, Ross AC, eds. *Modern Nutrition in Health and Disease.* 9th ed. Baltimore, MD: Williams and Wilkins; 1999:381-389.

Todd K, Butterworth RF. Mechanisms of selective neuronal cell death due to thiamine deficiency. *Ann NY Acad Sci.* 1999; 893:404-411.

Webster MJ. Physiological and performance responses to supplementation with thiamin and pantothenic acid derivatives. *Eur J Appl Physiol Occup Physiol.* 1998; 77:486-491.

Webster MJ, Scheett TP, Doyle MR, Branz M. The effect of a thiamin derivative on exercise performance. *Eur J Appl Physiol.* 1997; 75:520-524.